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QUARTERLY

THE CHICAGO MEDICAL SCHOOL

VOLUME 6. NUMBER 3

JULY. 1945
SEPT., 1945

BUY WAR BONDS

QUARTERLY

Published Quarterly Under the Auspices of

THE CHICAGO MEDICAL SCHOOL

VOLUME 6, NUMBER 3 JUNE-SEPTEMBER, 1945

CONTENTS

EDITORIALS 2

BEWARE OF VITAMINS 4
Piero P. Foa, M.D.

WAR AND PSYCHOSOMATIC MEDICINE 6
Don Shoemaker

LIQUID AMMONIA AND THE NITROGEN SYSTEM OF COMPOUNDS 7
R. G. Roberts, Ph.D.

PULMONARY HYPERTENSION AND COR PULMONALE 11
Emanuel Chusid

THE RELATION OF CHEMICAL STRUCTURE TO BIOLOGICAL ACTIVITY 14
Piero P. Foa, M.D.

ERYTHROBLASTOSIS FETALIS AND THE RHESUS FACTOR.....17
Wallace Salzman

SOCIAL NOTES 19

COMMENCEMENT 20

ALUMNI NEWS 21

LIBRARY 26

FACULTY NOTES 27

ORGANIZATIONS 28

ABSTRACTS 29

BOOK REVIEW 30

LETTERS TO THE EDITOR 37

Editorials . . .

THE PHYSICIAN FACES THE FUTURE

The war is at an end. Destruction, appalling in its extent, has left its stark, barren mark upon the face of the earth. Thousands of people in Europe will starve this winter. Epidemics of disease may well wipe out many more thousands of malnourished, ill-clad sufferers. The "four horsemen" of the Middle Ages will ride again unless their mounts are tethered from the start.

Amidst all this despair which inevitably follows in the wake of every major world conflict, the physician stands out like a mighty gladiator ready to battle the frightful monsters of pestilence and malnutrition.

In the past, he has performed creditably in all the major theaters of war in keeping down the incidence of infection and battle mortality. The problems which now face him are even more difficult. During the war, the enemy was fed, clothed and attended when sick or wounded by his own administrative officers. Now that the war is over, the enemy, in the interests of humanity, becomes as much our responsibility as our own men. Thus the already over-burdened physician is further laden down with an expanded and vastly more complicated program of medical care. The emphasis is now shifted from cure to prophylaxis.

Besides the problems in the occupied countries, the physician faces renewed problems right here in the United States. Returning veterans, especially those coming from the tropics, will bring back with them diseases such as malaria and filariasis, for which potential vectors exist in many parts of the country. It will be the physician's task to keep these diseases in check, either by destroying the vectors or by some new means as yet undeveloped.

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In addition to these general problems, the physician is faced with personal problems which to him are of almost equal gravity. The newly discharged medical officer must once again set up a practice. Those men who attempt to further their education first, by obtaining residencies, will find these positions difficult to obtain because of the abundance of applicants. The kaleidoscopic upheaval of the existing order is inevitably bound to effect the present method of medical administration. The physician must prepare to adjust himself to the new set-up which public opinion will insist upon.

It is readily apparent that we, as physicians, are faced with a grave and difficult future. But our unshakeable faith in our profession and in humanity will supply us with the courage to face these issues squarely, and see them through to a satisfactory conclusion.

ALUMNI NEWS

One of the permanent departments of our journal, which is constantly expanding with every issue, is Alumni News. From a single page in June 1941, it has today grown to be the largest single feature.

Many students now in school may not appreciate this section of the *Quarterly* as much as those departments dealing directly with events within the school. But any alumnus will vouch for the fact that this section is to him one of the most interesting and eagerly awaited features of the magazine. In it he reads of the achievements of his fellow graduates. Changes in rank, new appointments, marriages, births and deaths as well as other matters of great personal interest are all found here.

Because we realize how much the alumni look forward to this section, we take great pains in getting material for it. Letters from alumni are carefully read and the most informative and interesting are put aside to appear in the "Letters to the Editor" column. All data received is correlated and arranged according to year of graduation, in order that the reader may find his own class at once. Changes of address are handled by Miss Luebeck, the Dean's secretary, so that no alumnus, especially those in service, will miss out on a copy of the *Quarterly* due to incorrect address.

It is extremely important to remember, however, that this section of our magazine cannot continue to function without the active interest and participation of all of our graduates. This is strictly a cooperative enterprise.

We ask you, the alumni, therefore to keep us constantly informed as to your whereabouts, activities and distinctions. In this manner your former fellow classmates may obtain as much pleasure and satisfaction in learning of your progress as you derive from theirs.

BEWARE OF VITAMINS

Piero P. Foa

Assistant Professor of Physiology and Pharmacology

NUMEROUS articles on vitamins appear daily in the medical literature, but very few, if any, deal with the toxic action of these substances and with the untoward effects which follow the use of large repeated doses. Although it is true that clinical hypervitaminoses are relatively rare diseases, one must not forget that severe lesions have been produced in the experimental animal by quantities of some of the vitamins which are not too much greater than the therapeutic doses. One must also keep in mind, that, in a vitamin-conscious era, in which so many people take so many vitamins without medical supervision, and in which the long-established supremacy of the hot dog is being challenged by the vitamin pill, the cases of clinical hypervitaminosis will undoubtedly increase and the physician must be prepared to recognize them. The consequences of large intakes of some of the vitamins, such as Vitamin A and Vitamin D, have been known for a long time, others have been recently discovered still more will undoubtedly be recognized in the future, as the clinical use of new vitamins will become more common and a greater selection of them will be added to the already miraculous pills.

Vitamin A.—The experiments on the toxicity of Vitamin A date as far back as 1923 when Hopkins discovered that a moderate excess of cod liver oil is harmful to the rat unless it is "balanced" with an increase in the ratio of vitamins of the B complex. This observation was confirmed by Harris and Moore who fed a diet containing 15% cod liver oil to rats. The animals showed a decrease in the rate of growth, unkempt hair, paralysis of the legs and constantly kept an arched posture. The amount of Vitamin A administered in these experiments was approximately 1000 tomes greater than the minimal daily requirement and its ill effects could be prevented by feeding the rats an amount of B-complex 4 times as large as the minimum required for optimal growth. Later other observers added more symptoms to the list of those believed to be characteristic of hypervitaminosis A: loss of hair, hemorrhagic retinitis, pulmonary lesions, resorbtion and fracture of the bones, (Davis and Moore); sudden internal hemorrhages, pericarditis and anemia (Rodahl and Moore); glomerulonephritis, lesions of the spleen, the liver and the testes (Von Drigalsky and Laubmann); ocular hemorrhages, exophthalmus and pulmonary rales (Collazo and Rodriguez); myocardial lesions and cardiac decompensation with generalized congestion and death (Vedder and Rosenberg); inflammation of the oral mucosa and of the conjunctiva (Bauman and Moore); anemia, leucopenia, splenomegaly and erythroblastic hypertrophy of the bone marrow (Poumeau-Delille); increased excretion of calcium, decreased basal metobolic rate, increased blood lipids and blood cholesterol with the appearance in the liver and spleen of cells similar to those observed in the Christian-Schuller disease. The sudden hemorrhages which are the most common cause of death in the rat are due, according to Light and collaborators, to a decrease in the prothrombin concentration of the blood. This decrease appears about 10 days after the daily administration of 15,000 units of Vitamin A.

Hypervitaminosis A in man must not be confused with hypercarotenemia. The latter follows the use of large amounts of foods containing carotene in high concentration, is often accompanied by xanthosis of the skin, and, in most cases, requires no other treatment than a correction of the diet. Only rarely is hypercarotenemia associated with loss of weight, hepatomegaly, hypotension and asthenia (Joseph). A typical case was recently described by Henschen. A 49 year old woman, having eaten about 2 pounds of carrots a day for 6 months, developed a syndrome characterized by hepatomegaly, splenomegaly, hypochromic anemia, leucopenia, xanthosis and pallor of the skin, asthenia, dyspnea, paresthesias in hands and feet associated with a very high concentration of carotene in the plasma. True hypervitaminosis A is a syndrome which, although much rarer than hypercarotenemia, is, however, much more severe. A typical case was published recently by Joseph. A 3 year old boy had lost his appetite since the age of 18 months. The hair was dry and scarce, the eyebrows were lacking and so was the hair of the body, he had clubbed fingers and toes and the X-Rays showed zones of

rarefaction and vacuolization of the long bones. Spleen and liver were enlarged. The child, since the age of 3 months, had consumed approximately 240,000 units of Vitamin A daily plus an unknown amount of cod liver oil which he took directly from the bottle. Two months were necessary for the appetite to return to normal and for the hair to grow back and 6 months for the other symptoms to disappear, although at this time the plasma concentration of phosphate was still elevated and that of protein abnormally low.

The problem of whether toxicity of the vitamin A concentrate is due to Vitamin A proper or to other substances contained in the extracts has not been solved and for a discussion the reader is referred to the bibliography cited. Among the substances always present in cod liver oil and in vitamin A concentrates is vitamin D, which, as we shall discuss below, can also produce severe symptoms. Hypervitaminosis A and hypervitaminosis D, however, give a different clinical picture both in animal and man, and furthermore, Harris and Moore were not able to reproduce the lesions which they obtained in the rat with vitamin A concentrates by feeding the animals corresponding amounts of pure irradiated ergosterol. Light and collaborators and Herbst, Paveck and Elvehjem obtained the same results with vitamin concentrates or equivalent amounts of vitamin A purified by fractional distillation.

Vitamin B_1 or Thiamin—There are no indications that Thiamin is capable of producing a hypervitaminosis analogous to the one described above, although Klapp, Abels and Rhoads have recently demonstrated that an excess of thiamin produces an increase in the urinary excretion of riboflavin and may, therefore, produce a riboflavin deficiency. A somewhat similar mechanism may be the basis for the harmful effect of thiamin when used alone in the treatment of multiple vitamin deficiencies. If this is done the symptoms of pellagra (nicotinic acid deficiency) may become more severe (Singher and Coll.). Thiamin in large intravenous doses is toxic and can kill in a few minutes. According to Goodman and Gilman the toxic dose varies between 125 and 350 milligrams per kilo of body weight. The symptoms are weakness, tetany, shortness of breath and death due to respiratory paralysis. The toxic dose of thiamin is several thousand times greater than the therapeutic dose, and therefore, the therapeutic index is very high. It is possible, however, that the intravenous injection of 500 to 1000 milligrams of thiamin in a man might be dangerous, especially in cases predisposed to respiratory or cardiac failure. Experiments being performed in this laboratory, in collaboration with Dr. Jay A. Smith and Miss Harriet Weinstein, have shown that the intravenous injection of 50 to 100 millgrams of thiamin per kilo of body weight in the dog produces a rapid fall of the arterial pressure accompanied by tachycardia and cessation of all respiratory movements. In a very short time the pulse becomes very slow and arythmic and the animal dies. The electrocardiogram shows, among other changes, arythmia, decreased electrical potential and inversion of the T wave. Few of the animals can be saved by artificial respiration.

Vitamin B_2 or Riboflavin — There are isolated and not too convincing observations on hypervitaminosis B_2. It has been observed (Okey) that the daily administration of 25 micrograms of riboflavin, added to a diet which already contains 120 micrograms of the vitamin, produces gall stones in the guinea pig.

Nicotinic Acid or Niacin—Anybody who has ever administered nicotinic acid to a patient, parenterally or by mouth, is familiar with its vasodilatory action. This is accompanied by flushing and rise in skin temperature (Bean and Spies; Abramson and Katzenstein) and, sometimes, by nausea and vomiting. It is known also that this pharmacological action is a property of nicotinic acid and does not follow the administration of nicotinamide. Relatively enormous quantities of nicotinic acid (4 grams per kilo of body weight) produce convulsions and death in the dog (Rose and Robbins). In the first instance we are dealing with short lasting pharmacological action of little clinical importance, which can always be avoided by the use of nicotinamide. In the second instance we are dealing with a toxic action which nicotinic acid has in common with other pyridines and results from the administration of doses which could be given to a patient only by mistake. Recent experiments, (Handler and Dann; Foa, Foa and Field), however, have shown that if much smaller doses of nicotinic acid or nicotinamide are administered over a period of a few weeks to the rat, one can produce lesions of the liver and kidney identical with those of choline deficiency. The quantity of nicotinic acid sufficient to pro-

(*Continued on page* 35)

WAR AND PSYCHOSOMATIC DISEASE

Don Shoemaker

The greatest error of the physicians of Hellas is that they try to heal the body without the mind.—Socrates.

Only he who grasps the innermost nature of man can hope to cure him in earnest.
—Paracelsus.

IN the consideration of the psychological aspects of war psychosomatic disease assumes an important position. Aside from the need for recognition and therapy of mental disturbances among the military, valuable opportunity for study of the psychogenesis of disease is offered. The exaggerated emotional stress which war imposes upon the soldier frequently makes for a more distinct syndrome entity than that found in civilian patients. This paper deals only with psychosomatic disorders rather than with war neuroses as a whole.

Biological and neurological studies have shown that when the organism is forced to make a new adjustment to environmental requirements, the whole past history of the organism is involved. Although we are inclined to evaluate human conduct in the light of high cultural goals—man is still subject to simple biological needs. These biological demands are clearly expressed in the survival of primitive modes of response—instinctive patterns of behavior and conditional reflexes. The reflex architecture of the nervous system requires that the organism behave in the direction in which the reflexes are conditioned.

In war, conditions of life place a precipitate and overwhelming strain upon instinctive and conditioned endowments of man. It is not surprising that the visceral components of the organism respond first by functional disturbances, and later by actual pathological changes brought about through disturbed physiology.

It cannot be denied that man, consciously or unconsciously, prefers this somatic interpretation of his suffering rather than an admission to his doctor or even to himself that he is not the master of his mental and emotional fate. When emotion expresses itself in bodily manifestations, as it always does when strong, the patient tends to accept such manifestations as those of bodily disease.

We are indebted to Miller and Miller (1940) for the following outline of psychosomatic disturbances found in military medicine. Only a brief review of the field is possible in this paper.

- Cardiovascular disturbances
  - Effort syndrome
  - Hypertension (acute and thansient)
  - Tachycardia
  - Peripheral vasomotor disturbances
- Gastrointestional disturbances
  - Stress dyspepsia
  - Peptic ulcer
  - Emotional diarrhea
  - Mucous and ulcerative colitis
  - Spastic colon
  - Stomatitis (non-specific)
- Genitourinary disturbances
  - Nocturnal enuresis
  - Impotence
- Neurasthenia
- Thyrotoxicosis
- Prolonged pleural effusion
- Night blindness (epidemics, unrelated to nutritional deficiencies)
- Exacerbations of: Diabetes, hay fever, asthma, and other allergic disorders.

The effort syndrome, characterized by palpitation, fatigue, blurred vision, precordial pain, and fainting upon exertion, was first described by Hartshorne and Da Costa in 1864, following their observations during the Civil War. In 1918, Lewis described 13,000 cases in London among World War I soldiers, and identified the syndrome as a definite psychosomatic manifestation.

The gastrointestinal disorders of the soldier have been described by numerous writers, among whom are White, Gillespie, and Alvarez. The latter summarizes his remarks upon the subject by quoting the soldier's slang phrase for emotional agitation: "getting one's bowels in an uproar."

In 1918, E. W. White observed several cases of thyrotoxicosis among soldiers, the onset of which was preceded by a period of extreme shock. Later, Maranon reported the work of Basedow (1921), who studied 48 cases of men of World War I whose syndrome of thyrotoxicosis

(*Continued on page* 28)

LIQUID AMMONIA AND THE NITROGEN SYSTEM OF COMPOUNDS

R. G. Roberts

Associate Professor of Chemistry

LIQUID ammonia is pure NH_3 and it can be condensed from the gas by eight atmospheres of pressure at room temperature. The liquid boils at -33.4°C under one atmosphere of pressure and it can, therefore, be used as a refrigerating agent. Since it is rich in nitrogen it can be used directly or in the form of derivatives as a fertilizer. It can be oxidized to nitro and nitate compounds; and it is thus a precursor of certain explosives. These three fields of usefulness have received great commercial exploitation. Our concern with liquid ammonia is described by the present paper, however, has to do largely with its use in research.

When ammonia gas is bubbled through water, ammonium hydroxide, a basic compound is formed rapidly. This ammonium hydroxide is the spirits of hartshorn or the volatile alkali that was described by the alchemists of the middle ages. They prepared it by distilling organic material, preferably deer horn or hartshorn. The process depends upon the use of a still which was an invention of the middle ages.

The term ammonia was apparently derived from sal ammoniac which yields some ammonia on dry heating, or more in the presence of a metallic alkali; and sal ammoniac or salt of Ammon can be traced back to the days of the ancient Egyptians. The Egyptian God of reproduction or life Ammon, Ammon Ra, or Jupiter Ammon, who was depicted as having a rams head with plenty of horns (a possible correlation to hartshorn and salt of Ammon), was honored by having a famous oracle in Lybia named after him. These ancient oracles were often placed where fissures in the earth existed and from which fumes escaped. The inhalation of the fumes would cause the person inhaling them to have visions (unless he inhaled too copiously). Sal ammoniac or ammonium chloride is often found near the craters of volcanoes, so it is not unlikely that it might have been found also around the "fuming oracles" of the ancient world. The oracles were sacred places of worship and so salt found in their vicinity would have unusual significance. Sal ammoniac or sal ammoniacum was described by the Roman historian Pliny, but judging from his description of the crystalline form, it is doubtful if the sal ammoniacum of the ancients was really ammonium chloride. More than likely it was nothing but a mixture of various ammonium salts and in some cases nothing but common table salt, or sodium chloride. At any rate, Egypt remained as the manufacturing center of sal ammoniac until the 15th century, when Basil Valentine, an alchemist, prepared ammonium hydroxide by passing the distillate from organic matter into water; and he and others showed that this volatile alkali would react with hydrochloric acid to form sal ammoniac. Also it was shown at about the same time that the gaseous fumes from the destructive distillation of organic matter would react directly with the fumes from hydrochloric acid to form sal ammoniac. This achievement was really a "rediscovery" of the Egyptian process for making sal ammoniac, for the Egyptians had been using the dried dung of camels, donkeys and horses as a fuel for hundreds of years and they discovered (no one knows just when) that if the soot from these dung fires were collected and placed in an earthen jar over which an earthen flower pot was held in position, that upon heating the jar, a white salt would collect in the cooler pot. This white salt, they thought, was the same as the white salt that had been found at the oracle of Ammon, so it was also called the salt of Ammon. What the Egyptians had really discovered was the process of sublimation, since ammonium chloride sublimes at 520°C and recombination would take place in the "flower pot" or condenser. Also NH_3 and possible acid-forming radicals would be obtained from the breakdown of organic matter. The Egyptain alchemists claimed that the best yields were obtained from dung excreted during the spring months of the year, indicating a possible dietary influence.

Ammonia gas was discovered by Priestly in 1774. This discovery was made possible because Priestly collected the distillate over mercury instead of water as had been done by Valentine. The molecular structure of ammonia was determined by Bertollet in 1780 and the gas was liquefied by Faraday in 1823. Of course, am-

monia is no longer prepared from dung or deer horn. The destructive distillation of coal supplanted the older methods and distillation has been replaced to a great extent by the so-called synthetic methods. In countries where cheap hydro-electric power is available the electric arc and cyanamide processes are used. In the presence of the electric arc, hydrogen and nitrogen combine directly to form ammonia:

$$3H_2 + N_2 = 2NH_3$$

In the electric furnace:

$$CaO + 3C = CaC_2 + CO$$

then at 1000°C the calcium carbide CaC_2 and N_2 combine to form calcium cyanamide $CaCN_2 + C$, and the $CaCN_2 + H_2$ superheated forms $CaCO_3 + 2NH_3$. The process by which the most ammonia is produced, however, depends upon the direct union of hydrogen and nitrogen at high temperature, 500° to 700°C, but below 700°C where NH_3 decomposes, and at high pressure, 150 to 200 atmospheres (Haber or Cesale) or 1000 atmospheres (Claude) in the presence of catalysts, such as iron, or various combinations of metals. Since 3 volumes of hydrogen combine with one volume of nitrogen to form two volumes of ammonia, it is obvious that high pressures are desirable in accordance with the law of mobile equilibrium. At 200 atmospheres the yield of ammonia is about 8%, while at 1000 atmospheres the yield is about 40%. The ammonia is recovered by liqefaction or by absorption in water.

As the age of the alchemists grew dimmer and the age of the chemists grew brighter, men of science such as Davy, Faraday and Bertollet became more and more interested in the chemical properties of ammonia. Davy had previously isolated metallic sodium (1807) from moist sodium hydroxide by his new electrolytic process. Since ammonia gas forms an alkaline solution when it is passed into water, Davy concluded that ammonia was a metal also. He tried to isolate the ammonium radical in a pure form by every means that was available in his day, but he was unable to do so. He finally succeeded, however, in trapping the NH_4 radical in the form of an amalgam by making the cathode in his cell of mercury. The ammonium amalgam did in fact exhibit many alkaline properties. Many years later in the early part of the twentieth century, McCoy at the University of Chicago succeeded by using a somewhat similar method in isolating tetra alkyl derivatives of ammouium. These alkyl derivatives also exhibit strong metallic properties. Following the very general solubility rule that like dissolves like, Weyl (1864) and Gore (1872) attempted to dissolve some of the metals in liquid ammonia. All of the alkali metals and calcium of the alkaline earth group dissolved forming blue solutions, and when liquid ammonia was permitted to boil away the bright metal remained in an unchanged condition, much to the surprise of the investigators. These workers along with Seely and Joannis made a study of the solubility of more than 250 elements and compounds. Liquid ammonia was not available for purchase on the chemical market of their day and they made their solubility studies in strong V-shaped test tubes, one limb of which contained the substance to be tested and the other limb ammoniated calcium chloride. The chemicals were added through an opening at the apex, which was then sealed and the limb containing the ammoniated calcium chloride was heated, while the limb contining the sample was cooled. Ammonia gas was thereby liberated in the limb containing the reagent and condensed as liquid ammonia in the limb containing the sample. It was a slow and tedious method, but it worked.

The story of research in liquid ammonia then shifted from England and the Continent to the United States. Hamilton Perkin Cady was studying inorganic chemistry under the direction of Edward Curtis Franklin at the University of Kansas. The year of 1896 Franklin had assigned to Cady the task of preparing some of the cobalt amine salts and of analyzing the preparations. Cady completed the preparations and analyses and then predicted, from his recently gained experience, that the ammonia in these and other salts containing ammonia must function in a manner very similar to that of water in salts with water of crystallization. He suggested furthermore, that liquid ammonia would probably be found to resemble water in its physical and chemical properties. As a direct consequence of Cady's remarkable prediction, who at the time was scarcely old enough to vote, has arisen a half century of productive research in liquid ammonia and the coining of the term "Nitrogen system of compounds."

The three most highly electronegative elements are fluorine, oxygen and nitrogen. This electro-

negativity gives these elements and the compounds formed from them certain characteristics in common. For example, their hydrides are highly associated. This association is brought about through the formation of hydrogen bridges. In water, which is the hydride of oxygen, the following association occurs:

H H H H
O.HO.H.O.H.O.H

Likewise in liquid ammonia:

H H H
H.N.H.N.H.N.H
H H

In this way millions of such molecules can be held together or associated through the hydrogen bridge or bond, where the hydrogen "appears" to have a valence of two. Some authors prefer to regard the energy involved in a hydrogen bridge as being created by a stabilization brought about by resonance, where the resonace may be regarded as an "electronic" tautatermization, as it were. The energy in an .H. bond is only 5 to 10 K cal. per mole as compared to 25 to 100 K cal. per mole for other linkages, but it is sufficient to give water and liquid ammonia very high boiling points for such simple molecules. By comparison,

H
methane H.C.H boils at -161.5°C. Furthermore,
H

the dielectric constants of water (80) and liquid ammonia (22) are extremely high (by comparison, benzene is 7) and, second to water, liquid ammonia is the best solvent known for either inorganic or organic compounds. The comparison can be carried out for many other constants and such data can be found in vaious critical tables. In chemical reactions also many similarities exist. For example, potassium amide, KNH_2, is as strongly basic in liquid ammonia as potassium hydroxide, KOH, is basic in water, Likewise ammonium chloride is as acidic in liquid ammonia as HCL is acidic in water. These many similarities led Franklin to state that there existed a "Nitrogen system of compounds" wherein nitrogen plays the same dominent role that oxygen plays in the compounds wherein it is found, and that often the course of a reaction can best be predicted or interpreted if one takes into account the "system" in which the reaction occurs.

On account of its remarkable properties as a solvent and dispersing medium and the ease with which it can be removed when the reaction has been completed, liquid ammonia has been used for carrying out hundreds of researches. These researches have been reviewed at various times in Chemical Reviews. In the present article, however, only a few of them can be mentioned and for the most part these shall be taken from researches on biological compounds and which, in several cases, were carried out in the chemical laboratory of The Chicago Medical School.

When a worker starts out on a new piece of research, he never knows, a priori, just where the research will lead him. It sometimes happens that discoveries will be made in fields far removed from the one originally chosen. As an example, a research was being carried out on various amino acids, peptides and proteins to determine the quantity of acidic hydrogen that would be evolved from each compound when metallic sodium was added to it after the compound had been dispersed in liquid ammonia. When various quantities of sodium are added to such compounds, a corresponding quantity of hydrogen will be liberated, depending, however, upon the nature of the acidic groups in the compound. By correlating the quantities of metal added and gas evolved a characteristic curve can be drawn for each compound, and by proper interpretation of the various curves one can postulate, at least, concerning the presence of certain groups within the large molecules; to wit, the diketopiperazine ring in peptones and proteins. This work was completed and the results when published indicated that peptones are richer in diketopiperazines than are proteins. (J.A.C.S. 56, 935 (1934) and 58, 309 (1939) and 61, 3554 (1939). However, an unexpected thing happened during the course of the work. When the conjugated protein hemoglobin was used, the hydrogen gas continued to be evolved as long as sodium was being added to the reaction flask. In other words, the reaction never seemed to come to a finish. The presence of a catalyst was suspected. Therefore, various constituents of the hemoglobin molecule were added separately to the reaction flask. the protein globin was tried first, but it reacted in much the same way as other proteins react. Next hemin was added and it reacted as hemoglobin had done but even more vigorously and the hydogen being evolved never seemed to stop. Next porphyrin was tried and very little hydrogen was liberated; obviously

there was nothing left but the iron. A piece of iron rodding was tried next, the results were positive but weak. Pyrophoric iron was better than iron rodding, but weaker than hemin. Following these trials, dozens of iron salts were tried. Some were better and some weaker than hemin. Among them ferric chloride, ferric sulfate and ferric nitrate proved to be the best. These results were somewhat puzzling since ferric nitrate is exceedingly soluble in liquid ammonia, while ferric sulfate along with all the other sulfates, including ammonium sulfate, is absolutely insoluble in liquid ammonia. At any rate, in the presence of these iron salts:

$$Na + liq.NH_3 = NaNH_2 + H_2$$

It is the sodium amide that lends importance to the discovery, since sodium amide is an important intermediary in the manufacture of certain drugs and dyes. Formerly it was made by passing ammonia gas into molten sodium. The apparatus used was bulky and expensive and the sodium amide was formed in large and hard lumps, which had to be pulverized under oil to prevent an explosion. When prepared in liquid ammonia by the aid of iron catalysts, the sodium amide forms in an extremely fine powder and furthermore, some of the drugs and dyes can be prepared in liquid ammonia also. In chemical parlance the process is a "natural." The invention was patented (U. S. Patent No. 2,163,100) and it was sold to E. I. duPont de Nemours and Company. However, eight years elapsed between the times of the original observation and the sale, three years of which involved a costly interference suit. It is well to remember that patents are "meat" for many others besides the inventor.

Another example of the usefulness of liquid ammonia in research was proven in the purification of curare. The drug was first used as an arrow poison by the Indians of the Amazon jungles, since it paralyzes muscular activity and thus aids in overcoming enemies or in killing prey for food. Of late years, it has found a use in medicine in lessening the severity of convulsions that accompany shock therapy, which is widely used in the treatment of certain mental disorders. As prepared by the Indians the drug is impure, containing much tar as the least harmful possibility and snake venoms as the worst. The crude curare has the appearance of pulverized black glass. It was found that in liquid ammonia the tar and other impurities were soluble, while the active principle was quite insoluble. Therefore, by using sintered glass filters in a closed system of Dewar flasks a good fractionation was obtained and the curare remained as a white powder. Curare is not very soluble at a neutral pH, but when glycine is added to it in liquid ammonia, a derivative is formed which is water soluble and less toxic and more prolonged in action than curare. The complete method has been published (J. Pharm. and Exp. Therap., 74, 392 (1942)) along with tables of data based on bio-assays.

Just as chemical reactions are sometimes reversible, so methods of discovery are reversible. A study of the acidic hydrogens of hemoglobin led to a discovery of an inorganic catalyst and a study of the acidic hydrogens of aliphatic acids and amino acids led to the discovery of a conjugated hormone that gives a prolonged elevation of blood pressure. In liquid ammonia one gram atomic weight of glycine in the presence of an excess of sodium will liberate one gram atomic weight of hydrogen. One gram atomic weight of tyrosine under like conditions will evolve one and one-fourth gram atomic weights of hydrogen, indicating that the phenolic group of tyrosine as well as its carboxylic group is acidic in liquid ammonia. When the two amino acids are mixed in equi-molar concentrations, one would expect the evolved hydorgen to be additive. Such is not the case, however, but considerably less than the calculated amount of hydrogen is evolved. This result might indicate a reaction between two such amino acids. As an additional check upon this type of reaction, adrenalin was substituted for tyrosine since it resembles the latter somewhat in structure and because its activity as a pressor substance can be followed by bio-assay. It was found that adrenalin does react in liquid ammonia with amino acids such as glycine to form a new derivative or conjugate which gives a much more prolonged elevation of blood pressure than adrenalin itself. This work was published in 1934 (Proc. Soc. Exp. Biol. and Med. 31, 998 (1934) and patented in 1942 and 1943 (U. S. Patents 2,275,809 and 2,333,581). The publication in 1934 antedated the publication in 1936 by Hagedorn and Jenson (J.A.M.A. 106, 177 (1936)) in which they described the preparation of a prolonged acting insulin. These are the earliest

(*Continued on page* 37)

PULMONARY HYPERTENSION AND COR PULMONALE

Emanuel Chusid

Pulmonary hypertension, acute or chronic, may be characterized pathologically by right ventricular dilatation and hypertrophy; etiologically, most commonly by left heart failure, mitral valve deformity, pulmonary embolism, and by chronic pulmonary fibrosis; and clinically, by signs of right ventricular hypertrophy, pulmonary conus dilatation, venous congestion, and of the underlying pathology.

Pulmonary hypertension occurs most frequently (either rapidly or gradually) from left ventricular dilatation and failure; somewhat less frequently, from mitral valve deformity; thirdly, and rather frequently, from massive pulmonary embolism (always acute); fourthly and infrequently in more than a slight degree, from severe chronic pulmonary disease (this is always chronic); fifthly, from the more marked grades of chest deformity due to high degrees of kyphoscoliosis or compression of the heart by funnel chest; and last, and very rarely, from primary diseases of the pulmonary arteries and arterioles. 1. 2.

Miscellaneous causes are: obstruction to pulmonary circulation by metastatic malignancy; by severe degrees of diaphragmatic herniation; and by sudden perforation of an aortic aneurysm into the pulmonary artery. 3. 4. Some congenital heart conditions will give rise to a pulmonary hypertension.

Cor pulmonale may be defined as pulmonary hypertension resulting from obstruction of the pulmonary circulation.

The reported incidence has shown some variations. White and Jones have reported an incidence of 0.9 percent in 2,314 cases. Scott and Garwin have reported 6.5 percent of 790 cases who died of heart diseases. These reports are of chronic cor pulmonale . . . the acute form is a more recently observed clinical entity. 5. 1.

In left ventricular failure the left ventricle is incapable of pumping its usual amount of blood. If the right ventricle is not in failure, the pulmonary circulation becomes engorged, and hypertensive. If the process is acute this will lead to right ventricular dilatation and failure and will give rise to the secondary symptoms and signs described in the section on acute cor pulmonale (the primary signs and symptoms being those of left ventricular strain); if the left ventricular failure is slow, the right ventricle may become hypertrophied and may fail. The signs and symptoms are secondarily those of the cardiac aspect of chronic cor pulmonale which will be discussed later.

In mitral stenosis, the stenosis of the mitral valve causes a back pressure into the pulmonary circulation. This may result in right ventricular hypertrophy and dilatation and will secondarily give signs of chronic cor pulmonale (the primary signs and symptoms being those of the stenosis).

Acute cor pulmonale. 1. 6. 7.

Acute cor pulmonale has been defined by McGinn and White as a condition where sudden massive obstruction of the pulmonary circulation causes a dilatation of the right ventricle. The cause is almost always massive pulmonary embolism; the embolus coming from the large veins of the lower extremity, the pelvis and the abdomen. It has been caused by perforation of an aortic aneurysm into the pulmonary artery, the increased pressure in the pulmonary artery causing right ventricular dilatation; and there are reports of acute cor pulmonale as a result of sudden severe herniation of abdominal contents through the diaphragm. Acute respiratory diseases do not give rise to acute cor pulmonale. 8.

Acute cor pulmonale occurs in the older person, that is, the age group most likely to have pulmonary embolism. Both sexes are about equally affected. 8.

The major predisposing factor is venous thrombosis in the deep veins of the leg; and the factors which lead to this condition such as stasis, and phlebitis in a patient who has submitted to surgery (particularly abdominal surgery) are of particular importance.

Pathological findings in acute cor pulmonale are those of right ventricular dilatation, pulmonary artery dilatation, pulmonary embolism (enough to block sixty percent of the pulmonary circulation or more), and venous thrombosis in the legs or abdomen. White has found that there is either a rider embolus in the bifurcation of the pulmonary artery or there are two large emboli, one in each lung.

At autopsy the right heart may not be found to be dilated due to the subsidence of the functional dilatation. There may also be signs of congestive heart failure. Death is frequently due to shock.

There are no symptoms of the acute cor pulmonale, *per se*. The symptoms that may occur are probably masked by the symptoms of pulmonary embolism. The substernal oppression, however, may be due to the acute cardiac dilatation. Otherwise the symptoms found are: the state of shock, the severe air hunger, substernal oppression, cough, weakness and syncope (sometimes). Later symptoms, if the patient lives, are the fever, pain in the chest (due to pleuritis), and epigastric discomfort (due to hepatic engorgement secondary to heart failure). 7. 8. 9.

Signs of acute cor pulmonale are those of right heart enlargement, pulmonary artery enlargement, and of heart failure. These signs may be diminished or masked by insufficient venous return to the right heart due to a state of peripheral shock which frequently accompanies pulmonary infarction.

Signs of pulmonary artery enlargement, by virtue of the increased pulsation, are evident on inspection, palpation and percussion over the pulmonary area. On auscultation, P2 is accentuated. There may be a loud blowing pulmonary systolic murmur, and a to-and-fro friction rub.

Signs of right ventricular dilatation and failure are increased dullness on percussion, engorgement of the neck veins, and sometimes signs of enlargement of the liver. 9.

The acute cor pulmonale gives rise to an electrocardiographic picture which is said to be almost pathognomonic. 6. 8. 9. This includes:

1. An S wave in lead 1
2. A low or inverted T2
3. A marked Q3
4. An inverted T3 and T4
5. An elevated ST segment in lead 3.

These changes are attributable to the acute dilatation of the right ventricle, and they may come and go, as does the dilatation. About one-third of the patients having pulmonary embolism will show these signs. Sometimes the electrocardiographic picture is combined with that of myocardial infarction which is sometimes precipitated by pulmonary infarction. Should this occur, an exploratory precordial lead would reveal the acute cor pulmonale. 9.

No X-ray studies of this condition have as yet been published.

The pulse may be regular and rapid, the arterial pressure low, and the venous pressure high.

Pulmonary embolism must be thought of when there are recurrent episodes of chest discomfort, dyspnea, tachycardia, fever, or bloody sputum. Often, only one or two of these symptoms may appear.

In many cases the condition is transient, but death may occur due to: (1) the vasomotor shock, (2) repeated pulmonary embolism, or (3) heart failure. The main complications of the disease are vasomotor shock, cardiac infarction due to myocardial ischemia, and congestive heart failure. Frequently, pulmonary embolism will complicate chronic heart disease and will be the immediate cause of congestive failure. 9. 8.

Immediate treatment is bed rest, ¼ grain morphine subcutaneously, and oxygen inhalation. Digitalization should be tried in the advent of right heart failure. The thrombosed veins should be searched for and ligated. A contrast media may be necessary to locate the thrombus. 1.

Acute cor pulmonale may be confused with (1) acute coronary occlusion and accompanying left ventricular failure, with (2) congestive heart failure due to heart disease, and with (3) pulmonary infectious conditions. These conditions may be ruled out by means of a careful history and an electrocardiogram. Spontaneous pneumothorax and spontanious mediastinal emphysema may be easily ruled out in physical examination.

Chronic cor pulmonale

Many etiological factors have been discovered to give rise to chronic cor pulmonale. All of these involve obstructive lesions to the pulmonary circulation. In approximate order of frequency, these are: 1.

(1) Pulmonary and pleural lesions involving extensive pulmonary fibrosis (particularly from silicosis).
(2) Marked emphysema; (this is disputed by Schiller I. W. and Colmes). 11.
(3) Tracheal or bronchial stenosis.
(4) Pulmonary collapse (in infancy, failure of the alveoli to develop).
(5) Chronic inflammatory conditions of the lung parenchyma.
(6) Mechanical factors resulting from chest deformities.
(7) Other intrathoracic conditions such as

lymph node enlargement causing obstruction to the pulmonary circulation.

(8) Large fibrosed thrombi originating as pulmonary emboli, the immediate effects of which, the patient has recovered from.

(9) The pressure of a syphilitic aortic aneurysm on the pulmonary artery causing an obstruction. (Garvin and Siegel, 1939.) 10.

(10) Primary endarteritis obliterans of the pulmonary arteries. (Ayerza, 1901; Arrillaga. 1912.) Because of the deep cyanosis that has been seen in a few cases of this type. the patients have been sometimes called "black cardiacs."

White and Jones report 17 out of 21 cases of chronic cor pulmonale were over fifty. Scott and Garwin (1941) report that 35 cases out of 50 were over fifty. It can be seen that the disease occurs mostly in older people. Incidence of primary pulmonary endarteritis is younger, the condition being found mostly in young and middle-aged men. White reports one death of a boy at the age of 11. This is probably the lower end of the range of age of incidence.

The male is much more susceptable to chronic cor pulmonale than the female. In Scott's 50 cases, 48 were males and only two were female. Of 25 cases of chronic cor pulmonale found at the Massachusetts General Hospital in the ten-year period of 1932 to 1942, 20 were males and only five were female. The preponderant occurrance in males is probably due to the greater occurrance of chronic pulmonary diseases.

The predisposing factors of cor pulmonale in the chronic form are those of chronic pulmonary disease. These are climate, poverty, malnutrition, and hereditary influence. The most common predisposing factor is pneumoconiosis (especially anthracosis and silicosis). 12.

The essential pathology of chronic cor pulmonale is that of pulmonary artery dilatation, right ventricular enlargement and in later stages, right auricular enlargement, and congestive failure. The right heart enlargement is due, at first, to hypertrophy of the myocardium (hypertrophy of the individual muscle fibers), and later, to dilatation of the right ventricle due to myocardial weakness. This leads to tricuspid insufficiency and right auricular dilatation. With growing weakness of the myocardium, congestive failure sets in. 2. 15.

In a long-standing cor pulmonale, atheromatous plaques may be found in the pulmonary arteries. Other pathological findings in the pulmonary arteries are primary endarteritis obliterans (a rare cause of cor pulmonale), which shows up as an endothelial proliferation of these vessels. Treponema pallida has been reported to be a cause for this process. In most cases the cause of the proliferation is still unknown.

The left ventricle is not affected in chronic cor pulmonale, except in cases caused by mitral stenosis, where the left ventricle may be found to be slightly small (in recent stenosis), or hypertrophied as in a case of a long-standing stenosis.

Extremely rarely, a condition of failure of the lung alvioli to open, may be found in infants. 3. In this case the child has extreme difficulty in breathing, has an endarteritis, and a hypertrophy of the right heart. The child generally dies within the first year. Carcinomatous emboli causing vascular obliteration is another cause of cor pulmonale, and may therefore be a finding in the disease. 14.

The symptoms of chronic cor pulmonale are those of the underlying pulmonary pathology, if any, and those of right heart failure; due to congestion of the liver, gastrointestinal tract, and lower extremities. White contends that palpitation is not characteristic, and neither is pain except that due to the congested liver.

Signs of chronic cor pulmonale may be those of chronic pulmonary fibrosis, right ventricular enlargement, or congestive failure.

Signs of marked pulmonary fibrosis with emphysema are cyanosis, clubbing of the fingers and toes, polycythemia, lowered oxygen saturation of the arterial blood, restricted respiratory movements with prolonged and forceful expiration, low diaphram with limited excursion, barrel-shaped chest, and low vital capacity. 16.

It is often very difficult to determine right heart enlargement on physical examination. This is due to three main factors: (1) the position of the right ventricle is such that enlargement produces primarily an antero-posterior displacement which may not be observed on percussion. (2) The low diaphragm in chronic pulmonary disease may permit the heart to hang low giving an illusory smallness to the heart. (3) The emphysema found in chronic pulmonary disease makes the thorax hyperresonant thus making cardiac percussion difficult. 1. 16.

(*Continued on page* 36)

THE RELATION OF CHEMICAL STRUCTURE TO BIOLOGIC ACTIVITY

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Assistant Professor of Physiology and Pharmacology

NEW ASPECTS OF THE MECHANISM OF ACTION OF VITAMINS AND ANTI-BIOTIC SUBSTANCES

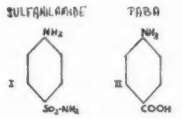
THE old topic of the relation of chemical structure to biological activity which recurs very often in Pharmacology and in other sciences, has recently acquired an entirely new and very interesting chapter dealing with the action of vitamins, enzymes and the antibacterial action of drugs.

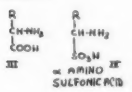
P-Aminobenzoic Acid and Sulfanilamide—The work under discussion originated with the observation of Woods that p-aminobenzoic acid (PABA) prevents the bacteriostatic action of sulfanilamide. The technic used in the experiments of Woods was very simple and its principles have been applied by most of the investigators who followed. A culture medium was prepared, in this case it was bacto-peptone, and enough sulfanilamide was added to inhibit the growth of streptococcus Hemolyticus for five days. If PABA was added to the culture growth would immediately start. Woods observed that PABA and sulfanilamide are very closely related from the standpoint of their chemical structures (I & II) and suggested that the anti-sulfa action of PABA might be due to a competition between the two substances at some vital stage of metabolism. When it was recognized that PABA is a constituent of all cells and a necessary growth factor, it was suggested that the antibacterial action of sulfanilamide was due to its ability to take the place normally occupied by PABA in the enzyme system of the cell. This would crowd out the necessary growth factor and inhibit the growth of the culture. The work of Woods was extended by Johnson, Green and Pauli who studied several derivatives and analogues of PABA and found that the chemical reactivity of the functional groups was of greater significance than the physical dimensions of the molecules so far as competition with sulfanilamide was concerned. An interesting corollary of this story was postulated by Mirick and demonstrated by Landy, Larkum, Oswald and Streightoff, namely, that sulfonamide resistant strains of staphylococcus aureus synthesize seventy times more PABA than do parent strains of the same organism, a quantity considerably in excess of the minimum amount required for reversal of the inhibitory action of the quantity of sulfanilamide to which S. Aureus is resistant. The antagonism between the two substances exists also in vivo, as Selbie found that PABA decreases the minimal lethal dose of S. Haemolyticus for the mouse and that five milligrams of PABA are sufficient to neutralize the bacteriostatic action of twenty-five milligrams of sulfanilamide.

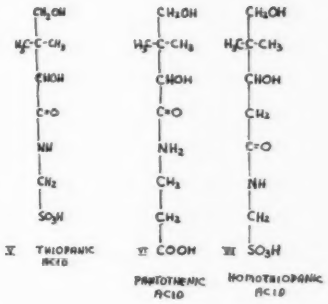
The competitive antagonism between PABA and sulfanilamide seems to rest in the substitution of the -COOH group of PABA for the -SO_2NH_2 group of sulfanilamide, the remaining part of the molecule being identical in the two substances. In a very similar way, McIlwain found that the aminosulfonic analogues of some amino acids, in which an -CO_3H group takes the place of the -COOH group, (III & IV), are capable of inhibiting the growth promoting property of the amino acid, and that this inhibition can be overcome by increasing the amount of the amino acid present in the medium. This is true, for instance, of valine and its sulfonic acid analogue. McIlwain (1941) made another interesting contribution, namely, that the greater is the need of the microorganism for a certain amino acid the greater is the inhibitory action of the amino acid analogue, and that when strains of B. typhosus or of S. aureus are trained to dispense with most amino acids, their growth ceases to be inhibited by the amino acid analogues. These interesting observations are consistent with the theory that the interference between the growth promoting substance and its analogue is of the type of a competition for the same spot in the bacterial enzyme system. Not only their analogues but also their homologues can act as antagonists of the amino acids, for instance, according to Pollack, the alpha-methyl derivative of beta-alanine neutralizes the growth promoting action of the latter.

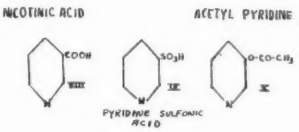
Pantothenic Acid—The substitution of a sul-

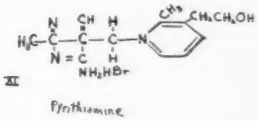
STRUCTURAL FORMULI OF SUBSTANCES DISCUSSED IN DR. FOA'S ARTICLE

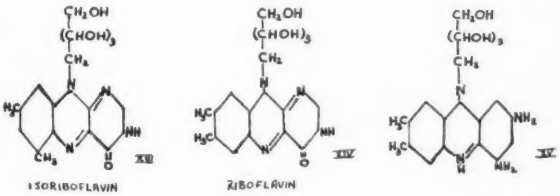


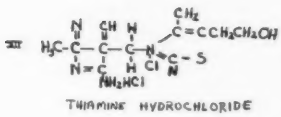


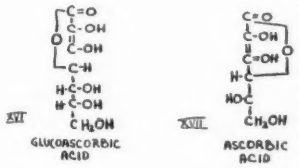


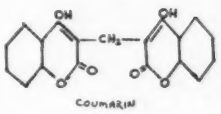


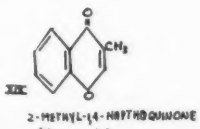












fonic acid group for a carboxyl group in the molecule of pantothenic acid will also produce a substance possessing growth-inhibiting properties in competition with pantothenic acid (V, VI & VII). The analogue probably screens the essential pantothenic acid away from its site of action. This fact was demonstrated first by Snell who found that the growth promoting property of pantothenic acid could be inhibited by its analogues: when L. arabinosus or yeast were used. Snell also found that E. Coli is inhibited by its analogue.

Essentially the same results were obtained by McIlwain (1942) who, using S. haemolyticus, studied the interaction of pantothenic acid and its analogue thiopanic acid and introduced the concept of antibacterial index, which he defines as the ratio of the minimal concentration of the inhibitor (CI) sufficient to prevent growth in the presence of a concentration (CM) of the growth-promoting substance. The antibacterial index (CI/CM) of thiopanic acid is 500 because 500 parts of the latter are necessary to neutralize the growth-promoting properties of 1 part of pantothenic acid. The antibacterial index of a given substance varies for different microorganisms according to the need for the growth-promoting substance being studied. According to Pollack also the alpha-methyl homologue of pantothenic acid inhibts the action of the latter on L. casei. A study of the relative concentrations of pantothenic acid and thiopanic acid in the blood of mice and rats was made by McIlwain and Hawking to determine the theoretic therapeutic activity of the latter and compare it with its actual activity in streptococcal infection of mice and rats. The authors found that thiopanic acid protects the rat if the dose is sufficient to keep the ratio of thiopanic to pantothenic acid in the blood above that necessary for complete bacteriostasis in vitro for at least 8 hours a day. One cc. of 25% thiopanic acid given 16 times in the course of 96 hours protected the rats against 10,000 minimal lethal doeses of S. Haemolyticus. The experiment in mice failed, but it was found that mice have a blood concentration of pantothenic acid about 10 times greater than that of rats and man and therefore the critical ratio had not been reached with the doses of thiopanic acid used. The fact that the effective ratio of the two substances is the same in vivo and in vitro indicates that the interaction is specific, that thiopanic acid starves the bacteria of pantothenic acid in vivo as well as in vitro and that the blood contains no substance other than pantothenic acid capable of interfering with thiopanic acid. The competition between thiopanic and pantothenic acids can be demonstrated also in forms of life higher than bacteria. Snell, Chan, Spiridanoff, Way and Leake were able to produce pantothenic acid deficiency in mice by feeding daily 200 milligrams of thiopanic acid per kilo of body weight.

Nicotinic Acid—The same structural difference existing between sulfanilamide and -aminobenzoic acid exists between nicotinic acid and pyridine-3-sulphonic acid (VIII, IX & X). The antagonistic action of the two substances was studied by McIlwain (1940). The results of his experiments indicate that pyridine-3-sulphonic acid inhibits the growth of B. coli and Proteus vulgaris and that this inhibition can be overcome by large doses of nicotinic acid. Woolley and White attempted the production of a nicotinic acid deficiency in mice by feeding pyridine-3-sulphonic acid, but failed. One must remember, however, that the mouse does not require nicotinic acid. When the experiments were repeated with dogs, it was found that, although normal dogs were not harmed by the analogue, they were killed if the diet did not contain nicotinic acid. Later Woolley and Collyer found that another analogue of nicotinic acid, namely, 3-acetylpyridine, produces in the mouse, a syndrome characterized by rapid breathing, loss of control of the hind legs, complete paralysis, emaciation, dry, red and inflamed skin and fiery red tongue. Death occurs in 3 to 14 days. The syndrome can be cured by the administration of proper doses of nicotinic acid. It is apparent that 3-acetylpyridine is a stronger antagonist of nicotinic acid than pyridine-3-sulphonic acid, as it can prevent the action not only of the nicotinic acid in the diet, but also of that which the animal synthesizes and can thus produce a nicotinic acid deficiency in the mouse, an animal which does not require nicotinic acid as a dietary factor.

Thiamine—Pyrithiamine is an analogue of thiamine containing a pyridine nucleus instead of the thiazole ring, (XI & XII). According to Robbins this analogue is capable of inhibiting the growth of fungi and this action can be reversed by thiamine. In this case one mole of pyrithia-

(*Continued on page* 31)

ERYTHROBLASTOSIS FETALIS AND THE RHESUS FACTOR

Wallace Salzman

It was no further back than 1939 that Erythroblastosis fetalis, responsible for 3% of fetal deaths, was a member of that group of idiopathic clinical syndromes which medical science had, as yet, been unable to explain. It was an unknown non entity, for it manifested itself in a manner which many other conditions did, making the problem a more difficult one to tackle. But in 1940 a clue to its pathogenesis was uncovered and since then, after exhaustive research, a simple incompatibility of mother's and fetus' blood has been shown to be the true cause.

The formation of antibodies with the presence of foreign proteins (antigens) in the blood is a protective mechanism against the invasion of the body by pathogenic microorganisms. This property of the blood, however, does not show predilection to microorganisms, but also maintains itself with any type of foreign protein which finds its way into the blood stream. If the foreign material should belong to a member of the same species, the reaction is termed isoimmunization, and with other species it is called heteroimmunization.

The presence of the common blood agglutinogens A, B, AB and O, have been recognized for many years, and blood transfusions, because of this discovery, have been made relatively safe, although undesirable reactions occur in some cases. In 1940 Landsteiner[1] discovered the existence of a factor in Rheus blood which was agglutinable by human serum. It was later found that this factor not only existed in the blood of the Rhesus monkey but also in the blood of 85% of the population; the other 15% was able to produce anti agglutinins when the factor was introduced into their circulation, but did not contain the factor themselves. It was later observed that 90% of the cases of Erythroblastosis fetalis were of children born of females who did not contain the factor, and fathered by males who did. This was the needed clue, and with scientific exactness on the part of the investigators a study was begun, and soon a simple genetic explanation was offered, which tried to explain the pathogenesis of this fetal condition.

The individual who has the factor is designated as phenotype Rh+, and that person without it is Rh—. Rh+ is considered to be a simple Mendelian dominant character, not sex linked. In a cross between an Rh+ male and an Rh— female, the first filial generation is not necessarily Rh+, thus showing the possibility of a heterozygous organization of genes. Landsteiner[2] thought it plausible to represent phenotype Rh+ by genotype (RhRh) or (Rhrh) and Rh— by (rhrh). If an Rh+ male with genotype RhRh is crossed with an Rh—female the child must be Rh+, but if the male has genotype Rhrh the child may either be Rh+ or Rh—. A punnet square representation of this can easily be made. (fig. 1.)

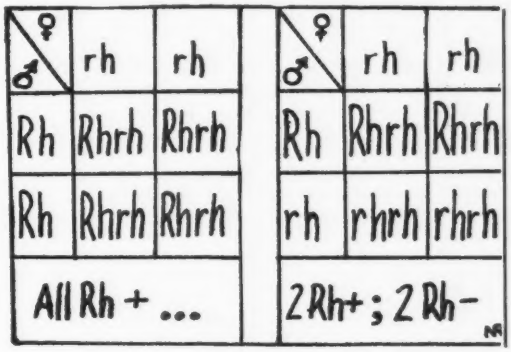


Fig. 1.

Erythroblastosis fetalis depends upon the difference in the fetal and maternal blood, the fetal being Rh+ and maternal Rh—. If, due to a defect in the placental barrier, the fetal blood finds its way into the maternal blood stream, an isoimmunization reaction takes place, since the fetal blood is antigenic to the mother's, and anti Rh agglutinin is formed. The same placental barrier can allow the maternal blood to enter the fetus' resulting in a hemolytic reaction. It is at this point that fetal erythroblastosis begins to manifest itself.

The pathogenesis simply stated is the response [3] of the Rh— mother to Rh+ fetal blood and the passage of the anti Rh agglutinin through the placenta to fetal blood causing hemolysis, but Davidsohn[4] did not stop there. He devised a scheme which makes one more easily visualize and understand the pathological progression of the condition. (fig. 2.)

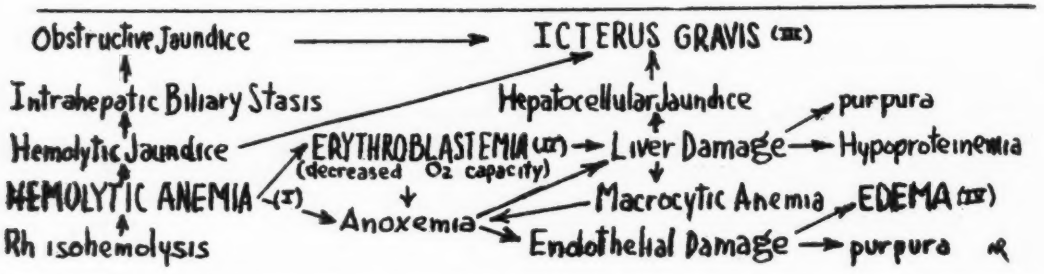


Fig. 2.

As can be seen by Davidsohn's diagrammatic representation, one of the striking features about fetal erythroblastosis is the wide variety of clinical entities in which it manifests itself. The most common is the Icterus Gravis type, followed in incidence by Hydrops fetalis and then the milder Hemolytic anemia. However, none of these entities are pathognomonic, for other diseases may show similar pictures. Davidsohn[5] feels there are 4 factors influencing the severity of fetal erythroblastosis and its manifestations. 1) The age of fetus when the Rh antibodies begin to act; 2) The length of time during which the fetus is exposed to such action; 3) The strength of the Rh antibodies; and 4) The permeability of the placenta. It is not unusual for the first child of an Rh—mother not to display symptoms, for maternal sensitization and utero wearing takes place during this period. It is the second child who first shows a more typical picture.

Hydrops fetalis[6] is fatal in 100% of the cases, the fetus being either a stillbirth, or one which expires shortly after birth, exhibiting extreme edema with effusion into the serous cavities. Icterus Gravis is manifested by a severe hemolytic icterus sometimes present at birth and reaching proportions not seen in physiological icterus. It can be distinguished from the latter by its early onset, or presence at birth. Hemolytic anemia may often exist without icterus and is found in those fetuses nearer their term. Possibility of damage to the nervous system and of later development of cirrhosis of the liver must be kept in mind in cases which recover; recovery depending upon the rapidity of transfusion of non-hemolytic Rh— blood to the fetus in order to supply the tissue already in O_2 debt.

Most constant finding at autopsy[7] is persisting hematopoiesis in liver, spleen and hyperplasia of bone marrow. Hemoglobin and RBC's are reduced but color index is above normal. The total number of nucleated cells is increased with an abnormally high ratio of early RBC's (normoblasts and erythroblasts). The placenta may reveal hematomas which may have been the direct cause of the fetal and maternal interchange of circulation.

According to Javert[8], mothers often exhibit signs and symptoms during pregnancy which may serve as a basis for suspecting Erythroblastosis fetalis in newborn fetus: 1) Multiparity 2) Rh negative mother; 3) Rh positive father; 4) yellow brown amnionic fluid; 5) excessive uterus enlargement; 6) premature labor; 7) Irish nationality; 8) increased icterus index; 9) disease in previous infant; 10) toxemia; 11) fetal distress before and during labor; 12) intrauterine death of fetus; 13) missed abortion; 14) systolic bruit of fetal heart in utero; 15) x-ray of fetus shows halo.

In order to completely cover this syndrome, it must be remembered that only 90% of the cases showed Rh negative mothers and an explanation for the other 10% is called for. Kelsall[9] feels that it is not illogical to explain many of the remaining cases of Erythroblastosis fetalis as due to an A.B.O. incompatibility. However, a more recent discovery is the Hr factor which was found to react distinctly with all Rh negative blood so that it apparently has some relation to Rh. It is most likely that this factor, using the same mechanism of isoimmunization, takes care of the great majority of the 10% of previously unexplained cases.

The Rh factor and its genetic picture that was first described by Landsteiner and discussed at the beginning of this article, is no longer as sim-

(*Continued on page* 34)

CASE No. 161—I heard one of your patients died from politeness. That's an odd cause of death. Major C. Ment. *Answer*: He was a deep sea diver—saw a mermaid—and tipped his hat.

RECTIFIED DIET

"You can't eat now," the nurse repeated "After a tonsil operation your throat has to rest."

But the patient was brashly insistent. Finally the exasperated nurse brought in a complicated apparatus, the most prominent feature of which was a long, red, rubber tube.

"Now," she said, "you're going to get fed," and rolled him over on his stomach, pulling down the sheet.

"Wait a minute," the patient protested, "that's not my mouth." But the tube was already in action. He subsided for a while. Then, "Hold on there."

"What's the matter now?" the nurse inquired.

The patient grinned impishly. "There's not enough sugar in the cocoa."

CASE No. 168 — You made a diagnosis on a patient and claimed he had population of the heart. You meant palpitation of the heart? Capt. B. B. Gunn. *Answer*: No. Captain, I meant population of the heart. He's a Mormon.

STINGY

Her husband stood by as I palpated the heart of a young woman affected with mitral stenosis. Concentrating on what I was about, I remarked half aloud to myself, "Yes, I get a thrill there." Whereupon Friend Husband barked, "Don't let it get you too much, Doctor, or I'll bop you one!" —*I. D. Stern, M. D.*

ODE TO A TERATOMA

From a Virginia Student

Oh! little lock of golden hair,
Why couldn't there be more body there?
What good are locks and perfect teeth
With nothing else at all beneath?
There should be arms and legs at least
On which our hungry eyes could feast.
Our eyes would gleam even more so
If there were just a little torso.
Instead our imagination stews
Over two such stimulating clues.
We'll never know just what we missed
When she became a dermoid cyst.

Social Notes

Norman Rosenzweig of the Class of 1945 was married to Carol Treleaven in New York, September, 1945.

David N. Yatzkan, '47, was married to Geraldine Lipman in Pittsburgh on June 17, 1945.

Seymour Levine, '47, was married to Lillian Konigsberg.

Sidney Malitz, '46, Ye Olde Editor, was married to Lucille Dvorsay of Hammond, on June 17, 1945, at the Stevens Hotel in Chicago.

Seymour S. Hodes was married to Evelyn Goeffrow at Chicago, August, 1945.

Joseph Zingher, '47, is the father of baby boy, born recently.

Janet Abraham was married to Stanley Menachoff, '45, on September 2, 1945, at Cincinnati, Ohio.

Ruth Plotnick was married to Morton Einhorn, '45, on September 15, 1945, at Chicago.

Florence Dicker was wed to Howard L. Kretchmer, '45, on June 17, at Chicago.

Murray Feldman, '45, married Mildred Milstone of Chicago on September 15, 1945.

Gloria Papo was wed to Eugene Dach, September 15, at the Statler Hotel in Detroit; and spent two weeks in New York.

Corinne Quint and Alan C. Siegel were married in New York on June 17, 1945, at the Hotel Henry Hudson.

Gerald Rabinovitz became engaged to Annajean Kornblatt on July 20, 1945.

Melvin Morrel was wed to Harriet Shapiro of Yonkers, New York, in September, 1945, at Park Central Hotel in New York.

Leonard Arnold and wife were blessed with twin boys on October 17, 1945, at 1:15 A.M., at the Norwegian American Hospital in Chicago.

Edith Petrone of Chicago was engaged to James Raia at her home on August 25, 1945.

Elizabeth Goldsmith, daughter of Maxmillian Goldsmith, '43, presently of New York, will celebrate her first birthday on November 23.

Arthur H. Rothenberg became engaged to Suzanna M. Susman of Chicago on May 23, 1945.

Martin Dillon was married to Phoebe Cohen in September, 1945.

Nat Sultan, '45, and Estelle Lichtenberg were married September 27, 1945, in Chicago.

(*Continued on page* 38)

Commencement

THE 31st Commencement Exercises of the Chicago Medical School was held in the 1st Congregational Church on September 15, 1945. 60 medical seniors received their degree of Bachelor of Medicine and were added to the already weakened ranks of the medical profession.

After the reading of the invocation by Reverend Charles Leslie Venable, an address was presented by Dr. Donald John Cowling, the president of the Carleton College and chairman of the Committee of Founders of the Mayo Memorial. The planning of a lasting peace was ably discussed by Dr. Cowling, who stressed the necessity of finding those natural Social Laws of the Universe which govern man's actions, just as we found the fundamental bases for the natural sciences. He suggested that unless we succeeded in finding these laws, just as a bridge would fall if basic physical principles are not followed, so would any structure created to maintain peace in this war torn world.

Dean John J. Sheinin presented the candidates to the Chairman of the Board of Trustees Mr. Charles H. Westbrook, who conferred the degree of Bachelor of Medicine.

Dr. John Evans, on behalf of the Board of Trustees, discussed the various achievements of the Chicago Medical School in the past year, emphasizing the effort of the students in behalf of the endowment drive. He ended his address by enumerating those men who had passed away, and a minute of standing silence was paid in tribute to these men of the medical profession.

With the reading of the Benediction the program ended and to the rhythmic chords of the Coronation March, the new doctors left the chapel.

The graduating students were:

William Harry Arnoff
Peter Allen Bakal
Irwin Theodore Barnett
Howard E. Berk
Edmund G. Brust, Jr.
Kenneth Miller Calhoun
Nunzio Cerasa
Robert James Corbett
Patrick James Cusack
David Oscar Dale
Garland Lee Dansby
Philip Deaver
Morton Einhorn
Russell Edwin Elmer
Murray Morris Feldman
Stanley Friedman
Lawrence Gluckman
Jerome Goldflies
James Patrick Griffin
Alvin Groupe
Frank Anthony Guida
Seymour L. Gurchin
Seymour David Guten
Herbert Louis Halper
Joseph Himmelreich
Leonard Horecker
Samuel Kahan
Murray L. Kaiser
Richard S. Kamil
Marshall Kanter
Harold Myron Kaplan
Howard Lyle Kretchmar
Arthur Richard Lane
Erik Larsen
Marvin Lerner
Michael A. Limosani
Max Linderman
Henry Wayne Maxfield
Stanford A. Menachof
Donald Dov Morrison
Clarence A. Peckler
Philip Porter
Nathan Rabison
Naftalie Rapoport
Burton Wolfe Rockliff
Marvin B. Rodney
Max Rothman
Harold Sanders
Henry Schnitman
Meyer Shapiro
Milton Silberman
Arthur B. Sincoff
Donald Evans Sloan
Harry A. Small
Nathan A. Sultan
Arvid A. Temple
Louise Tumarkin
Lawrence A. Weiss
Earl Bertram Zazove
Marvin Charles Ziporyn

Alumni News

1900—It is with deep regret that we are forced to announce the very untimely death of Dr. R. G. Olson. Dr. Olson passed away as the result of a pneumonia after a brief illness.

1915—Very welcome greetings have been received from Major William F. Bartlet. Major Bartlet is a former faculty member of our school as well as an alumnus. He is now in Santa Fe, New Mexico, where he has enjoyed meeting many of his former students.

1925—Dr. Walter W. Dalitsch was recently promoted from Lt. Commander to Commander in the United States Navy Medical Corps. Commander Dalitsch is now stationed in the Philippine Islands.

The Quarterly was very pleased to learn of the marriage of Dr. Julian P. Krakowski of Waterloo, Illinois to Miss Fern Zinser of El Paso, Texas. Our best wishes to Dr. and Mrs. Krakowski.

Back from the Pacific theater of operations and recipient of a medical discharge, Dr. Louis C. Novack dropped in for a visit recently. All of us wish Dr. Novack the best of luck in the resumption of his Southside practice.

It is with deep regret and profound sympathy that we announce the untimely death of Dr. Paul E. Sundwall of Waukegan. Dr. Sundwall served as county physician from 1938-1941, and was resident physician in Lake County General Hospital the following year. He died of a heart attack at the age of fifty-seven years.

1928—Captain Edwin C. Reynolds has just returned to the States after two years of service with the United States Army Medical Corps. Dr. Reynolds served in the Philippines and New Guinea.

1929—Rest in peace after service well done to your fighting comrades, Captain Walter E. Block. Dr. Block passed away while serving as physician in the armed forces of our country.

1932—Captain Sidney R. Bazell was a welcome visitor at the school during his recent visit to Chicago. Captain Bazell was on a well-earned furlough, his first after two and a half years in the Pacific theater of operations where he served in five major campaigns.

1933—Captain A. Kushner received the Purple Heart in November and has just been awarded the Bronze Star for work done while under enemy artillery and mortar fire and for the help he has given as a linguist. Dr. Kushner acted as a Russian interpreter on the Russian-German front.

1934—A welcome communication was recently received from Captain Andrew Krajec who informed us that he is stationed in Casablanca at the 38th General Hospital and was taking care of a WAC outfit. Dr. Krajec spent fifteen months in Italy with the 1th Army Air Force before being sent to Casablanca. We hope that Captain Krajec will soon be home to join his wife and three sons.

Captain Edwin J. Allen and Captain Norman S. Beebe were among the recent very welcome visitors at school. Both Drs. Allen and Beebe have been returned to the United States after seeing overseas service with our armed forces. To them and to all the other doctors serving in this war, those of us here at school say, "Good work, and may each of you return to your former private practices in the very very near future."

1935—Captain Patrick Parisi was recently awarded the Bronze Star in Germany. The citation was in recognition of efficient surgical service for the 740th Tank Battalion.

Captain William H. Borkenhagen has been awarded the Bronze Star for meritorious service in connection with military operations against the enemy during the period from June '44 to April '45 in France, Belgium and Germany. Captain Borkenhagen displayed expert surgical skill and mature judgment as battalion surgeon. Dr. Borkenhagen is attached to the 552nd Anti-Aircraft Artillery, Automatic Weapons Battalion.

To the friends and relatives of Lieu-

tenant Harry Tyllas, all of us join you in prayer for his speedy and safe return. Lieutenant Tyllas of the 101st Airborne Division has been reported missing in action since 1944.

Congratulations to Captain P. V. Hall for receiving the Bronze Star for Meritorious Service. Captain Hall is attached to the 108th Evacuation Hospital with the 9th Army. The decoration was presented on V-E Day which is also the birthday of his four-year-old son. As Chief of Anesthesia, Captain Hall and his staff have an enviable record of over 13,000 cases.

Congratulations, also, to Captain P. M. Garramone on his recent promotion. Captain Garramone is stationed at the Station Hospital, Savanna Ordnance Depot, Proving Ground, Illinois. How about looking us up sometime, Captain?

With deep sorrow we announce the death of Dr. Gordon Clarence McGary. Dr. McGary served in the armed forces for fourteen months and died of a heart attack at the age of 35. To those of us fortunate enough to know Dr. McGary, his memory will always live on.

1938—Dr. H. Paolozzi has now fully recovered from injuries received to his leg, and is now back with his unit, the 30th Field Hospital. Should any of his classmates care to write him, his APO No. is 403, c/o Postmaster, New York, N. Y.

1939—The School was very happy to be visited by Captain Morris Fox during his stay in Chicago, prior to leaving for his assignment overseas.

A very welcome letter has been received by The Quarterly from Lieut. George E. Fisher. Dr. Fisher proudly proclaims to one and all, "I have now been married one year and a half, and heartily recommend the institution."

1940—On a visit to the Windy City from way down South, Dr. B. G. Giel stopped in to say hello. Dr. Giel is Asst. Surg. (R) U.S.P.H.S. and is now stationed at Hazard, Kentucky, the Blue Grass Country. Keep up the good work, Dr. Giel, and don't let the mountaineers mistake you for a revenuer.

Long delayed greetings to everyone from Lieutenant Lawrence Kalom. Lieut. Kalom left the United States in 1943 and was in the Sicilian campaign where he was kept busy attending to the physical and mental illnesses of the men in his charge.

Capt. Samuel H. Coleman writes us that he has been transferred to Camp Butner, North Carolina, where he will serve in the capacity of Chief of Occupational Therapy and Physical Therapy at the Convalescent Hospital.

1941—Congratulations to Captain Joseph Geller on serving in the medical unit attached to the 3rd Army. In addition to being commended by General Patton, Capt. Geller's unit received the following praise from Col. Thomas D. Hurley, surgeon, "Your loyal, conscientious, untiring and highly efficient efforts in caring for casualties among your comrades in arms, has earned you their everlasting gratitude. Your services have evoked the highest praise and not only in this Army, but throughout the entire theater. I greatly appreciate your fine accomplishments in providing the 3rd U. S. Army with the best medical service in history." Captain Seymour Hershman was recently awarded the Bronze Star for meritorious service in connection with military operations against the enemy. Captain Hershman, serving as Assistant to Chief of Surgical Service, 109th Evacuation Hospital, distinguished himself by his outstanding performance of duty.

The Quarterly was happy to learn that Captain John M. Staron has returned from overseas and is stationed at the Schick General Hospital, Clinton, Iowa.

Captain Thaddeus C. Fijalkowski was a recent visitor at school. He had been assigned to the Pacific theater of operations and was leaving for a deserved rest in Florida.

Captain Nathan Frieberg was recent-

ly mentioned in *Yank*, the Army weekly newspaper, in connection with a very dangerous exploit in the Aleutions. Capt. Freiberg, with another surgeon, was taken aboard a tug after a 70-mile trip in a stormy sea, to remove the appendix of a stricken sailor. Dr. Frieberg was forced to operate without adequate equipment, using scalpels instead of scissors, and a glove finger for a draining tube, the operating table consisting of two boxes. The *Quarterly* expresses its highest admiration for Captain Freiberg's courage and ability in performing such a difficult and heroic task.

1942—*The Quarterly* proudly announces that Dr. Irving Blumenthal has recently been promoted from a First Lieutenant to a Captain in the Army Medical Corps. Captain Blumenthal is in charge of a batallion aid station on Saipan.

Lieutenant Alexander Jablonewski, who has been on limited service, has been given an honorable discharge from the Army Medical Corps.

1943—A card from Lieutenant Neil Esposito informs us of his change of address. The Lieutenant is now APO San Francisco. Good luck to you in your new post.

We are proud to announce the graduation of Lieutenant Arthur Howard from the Army's School of Military Neuropsychiatry. Lieutenant Howard received his commission in 1944 and has been on active duty since January 1944.

Lieutenant (j.g.) H. S. Glassman recently wrote us that he was stationed with the 7th Fleet, somewhere in the Pacific. Lieutenant Glassman related that Fleet Hospital was considered the best duty in the Medical Corps because of the excellent chance to practice medicine to its fullest extent. Our best wishes to Dr. Glassman.

The Quarterly was pleased to receive the announcement from Dr. S. M. Lilienfeld that he has opened an office at 718 West 63rd Street, Chicago, Illinois.

Announcement has been received of the birth of a baby, Harold Mathew Spinka, Jr., born to Lieutenant and Mrs. H. M. Spinka on April 2, 1945. May we extend our heartiest congratulations to you.

The Quarterly is happy to announce that Dr. Robert A. Berman and Miss George Anne Howie of Eau Claire, Wisconsin, were married on March 9, 1945. Dr. Berman recently completed his internship in New York City.

Dr. Louis Sena has opened an office in La Grange, Illinois. We are sure that he will find many people eagerly availing themselves of his excellent services.

Dr. B. J. Winston was a recent visitor at the school. Dr. Winston is taking a postgraduate course at the Cook County Post-Graduate School. He is engaged in a general practice in North Chicago and is now the proud father of a baby boy.

Our congratulations to Dr. Daniel C. Belden on the birth of a beautiful baby daughter, Robin Joanne. Dr. Belden is now practicing in New York.

Lieutenant (j.g) Harry F. Kaack of the United States Public Health Service, resorted to wireless instruction recently to bring relief from extreme pain to a crew member of a small fishing vessel, whose jaw bone was dislocated, while the ship was more than 200 miles off shore in the North Pacific. Lieutenant Kaack was contacted by the radio watch at the Coast Guard Juneau Harbor Patrol radio station, and using another person as his subject, gave a wireless demonstration on the manipulation required to snap the mandible back in place. After a period of intense waiting, during which time men on the ship attempted to carry out Dr. Kaack's directions, a faint message was received: "Medical advice carried out; man is now okay." Lieutenant Kaack enlisted in the Naval Reserve in October 1944. He is stationed in Juneau, Alaska, where he has charge of a naval hospital.

Asst. Surg. (R) Alvin Gross writes that he has been assigned to the Venereal Disease Division of the U. S. Public Health Service, and that he is stationed

at a Rapid Treatment Center in Meridian, Mississippi.

Lieutenant (j.g.) Irving N. Afrin, M.C., was sworn into the United States Naval Reserve, and reported to Camp LeJeune, North Carolina, in April.

Lieutenant (j.g.) Daniel Halpern, who received his commission in the Navy in March, is stationed at the San Diego Marine Base, San Diego, California.

The *Quarterly* wishes all the success in the world to Dr. Herbert Natkin who recently opened offices at 4010 W. Madison Street.

Lieutenant (j.g.) Raymond S. Rowlette, M.C., U.S.N.R., recently commissioned in the United States Naval Reserve, is attached to a Navy and Marine dispensary at Puget Sound. He writes that he likes the Navy and expects to be put to sea soon. Good luck, Lieutenant Rowlette.

Dr. Frank Uyeno has been appointed a field physician for the United States Indian Service. He is stationed at Pima Indian Reservation, Sacaton, Arizona, and he writes that the work is very interesting and pleasant.

1944—Lieutenant (j.g.) Turned Camp USNR has recently reported for duty in the Naval Dispensary at the Puget Sound Navy Yard in Bremerton, Washington, after completion of his internship at the Illinois Central Hospital in Chicago, Illinois.

Thank you, Lieutenant Weishaus, for your check to The *Quarterly*, and here is your insertion which you requested: Lieutenant (j.g.) James Weishaus, M. C., U.S.N.R., would like to inform his classmates that he entered service on July 10, and is temporarily stationed at the Navy Yard, New York.

Bernard Tumarkin, now serving internship, has received his commission as Lieutenant (j.g.) M.C., United States Naval Reserve. He hopes to complete his internship before being called to active duty.

Best wishes to Dr. and Mrs. V. V. Costanzo, who announce the birth of twin girls, Jacqueline Karen and Andrea Sherin. We are betting on the boys next time, doctor, so don't let us down.

1945—The *Quarterly* was very happy to receive the announcement of the birth of a son, Thomas Carroll, to Drs. Thomas and Sallie Tyrrell. Dr. Tyrrell is the former Sallie Jane Major. Loads of luck, Sallie. Congratulations to Dr. Milton Vainder on his recent marriage to Miss Patricia Evelyn Paley of New York. Dr. and Mrs. Vainder are at home at 3500 Lake Shore Drive, Chicago, Illinois.

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Alumni who hold offices as President or Secretary of County Medical Societies*:

Gallatin County

Dr. E. W. Burroughs (C.M.S. 1926)...President Shawneetown, Illinois.

Massac County

Dr. Vincent M. Timm (C.M.S. 1935)..President Metropolis, Illinois.

Stephenson County

Dr. Samuel H. Bess (C.M.S. 1938)....Secretary Freeport, Illinois.

White County

Dr. Lawrence R. Medoff (C.M.S. 1038) Secretary Grayville, Illinois.

Will-Grundy County

Dr. Joseph Trizna (C.M.S. 1936).....Secretary Joliet, Illinois.

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*As taken from the Illinois Medical Journal—August 1945.

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THE HUMOR OF OUR ALLIES

An English woman stopped in at an auction and there for a shilling and sixpence she purchased a most magnificent vessel. It was the largest she or anyone else had ever seen and the pink flowers around its middle as well as its size made it fit for a bishop's palace. She didn't mind at all carrying it home without wrappings and anyway she had to stop at the fishmonger's and it would be useful to carry the unwrapped fish home. So she marched in and setting it firmly on the counter she pointed a commanding finger and said "Ah pund ah fillet." The fishmonger stared with bulging eyes and replied coldly, "Ah pund ye don't, mam."

NEW COMMISSIONS

Lt. (j.g) Irving N. Agrin	C.H.S. 1943
Lt. Arnold L. Berger	C.M.S. 1943
Asst. Surg. (R) Eugene Brodsky	C.M.S. 1943
Capt. Max C. Cahan	C.M.S. 1939
Capt. Thaddeus Fijalkowski	C.M.S. 1941
Lt. (j.g.) Harold S. Glassman	C.M.S. 1943
Asst. Surg. (R) Alvin Gross	C.M.S. 1943
Lt. (j.g.) Daniel Halpern	C.M.S. 1943
Asst. Surg. (R) Nathan Horowitz	C.M.S. 1942
Capt. Leonid Kotkin	C.M.S. 1942
Asst. Surg. (R) Arthur L. Loebel	C.M.S. 1943
Asst. Surg. (R) Michael R. Sacks	C.M.S. 1943
Lt. (j.g.) Raymond S. Rowlette	C.M.S. 1943
Asst. Surg. (R) Herman L. Weisberg	C.M.S. 1943
Lt. (j.g.) Bernard Tumarkin	C.M.S. 1944

ADVANCE IN RANK

Capt. Edwin J. Allen	C.M.S. 1934
Capt. Philip N. Baker	C.M.S. 1940
Capt. Norman S. Beebe	C.M.S. 1934
Capt. Irving Blumenthal	C.M.S. 1939
Capt. Samuel R. Coleman	C.M.S. 1940
Capt. Nathaniel E. Landy	C.M.S. 1935
Capt. Harry Leventhal	C.M.S. 1939
Capt. Edward J. Levine	C.M.S. 1940
Major Samuel K. Lewis	C.M.S. 1933
Capt. Edward J. Maloney	C.M.S. 1939
Capt. Harvey H. Pettry	C.M.S. 1938
Capt. Samuel Pilchman	C.M.S. 1939
Capt. Melvin M. Rackloff	C.M.S. 1927
Capt. Leo D. Richey	C.M.S. 1941
Capt. James T. Slattery	C.M.S. 1934
Capt. P. M. Garramone	C.M.S. 1935

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PRECAUTION

The marine was just coming out from under anesthesia in the hospital tent. When he regained consciousness he noticed that all the tent flaps and window openings were securely fastened. A question revealed that it was still daytime.

Looking up at Major John Crawford, the doctor who had operated, the marine inquired why it was so dark when it was only afternoon.

"It's all right, soldier," said the Major, "we closed the place on purpose. There's a big fire not too far away. We didn't want you to wake up and think the operation unsuccessful."

* * * * *

Hang there like fruit, my soul, till the tree die!
—Shakespeare

New Books in the Library

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Journal of neurophysiology.

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If we could read the secret history of our enemies we should find enough of sorrowing and suffering in each man's life to disarm all hostility. —Longfellow

Library

TO THE NEWLY LICENSED PHYSICIAN

M. E. Campbell, *Librarian*

AS you sit waiting for the non-existent patient to arrive, you can console yourself with the thought that other physicians did likewise, and in their idle time many turned to other fields of endeavor both for money and amusement. Sad to say, by these by-products of leisure, they often became both famous and wealthy, while had they confined themselves to medicine, sad indeed might have been their lot; they would have died "unknown and unsung." Let me tell you a little of some of them.

RICHARD GATLING invented the Gatling gun (one method of getting patients).

DAVID LIVINGSTON was a famous African explorer of the mauve decade.

L. S. JAMISON of the infamous Jamison raid into the Transvaal.

GENERAL LEONARD WOOD, a famous soldier and one-time Governor of the Philippines.

THEODORE N. VAIL, the head of the Bell Telephone and originator of the automatic telephone.

As the profession of medicine seems to fit one especially to write, thru constant study and observation of mankind and their vagaries, I would recommend this field to you. When I tell you some of the famous names in literature who were physicians, you may have lit within you the lamp of a like ambition.

RABELAIS was born in 1490, studied medicine at the University of Montpellier from which institution he received his degree in 1530. He is known as a writer of broad tales, his stories are a mixture of insane mirth and mock gayety. He shows the childishness and also the grandeur of the commonplace. His most famous work is *Pantogruel et Gargantan.*

FRIEDRICH VON SCHILLER born in 1759 is known as a poet and dramatist, but he graduated in medicine and for several years was a military surgeon. Among his famous plays are *William Tell* and *Mary Stuart.*

JOHN KEATS born in 1795, one of the greatest poets of all time, was also a physician. He was apprenticed to Thomas Hammond, a well known surgeon in Edmonton, with whom Keats could not agree, so he studied elsewhere. He was a dresser at Guy's Hospital; while there he met Leigh Hunt and Shelley, and finally abandoned medicine for poetry in 1816.

OLIVER GOLDSMITH author of *Deserted Village* and the *Vicar of Wakefield* was a duly licensed doctor and wrote two medical books. He was of a miserable and vacillating disposition and changed his professions as one changes ones clothes. He began the study of medicine when twenty-four at Edinburgh; for a wonder he finished his course but soon his old restlessness returned. He was a jack-of-all trades, but unlike the old adage he was a master of literature.

SIR ARTHUR CONAN DOYLE began to write the Sherlock Holmes stories almost as soon as he began to practice medicine. He was unsuccessful in obtaining a hospital appointment, so went back and specialized in ophthalmology but his success in this field was short lived. Finally his great success with his stories made him desert medicine entirely and concentrate on literature.

ANTON CHEKHOV, a Russian, was a doctor-author and one of the greatest short story writers of the modern era. He practiced medicine during his early manhood, but tuberculosis curtailed his activities, so he turned to writing until his early and untimely death.

ROBERT BRIDGES, the late Poet-Laureate of England, wrote excellent medical papers before he began to write poetry. He has left as a monument some of the best of the modern English verse.

Among our Americans, we find

OLIVER WENDELL HOLMES who was almost as famous as a physician as he was an author. He is responsible for the coinage of the word "anesthesia" shortly after Doctor Morton's demonstration at Massachusetts General Hospital. He contributed to the study of puerperal fever and its prevention in a notable degree; as much so, some think, as Semmelweiss. He taught anatomy for forty years at Harvard Medical School, and was the first president of the renewed Boston Medical Library. It was during this time he wrote his famous poems and essays. At the Bos-

(*Continued on page* 35)

Faculty Notes

Dr. Piero P. Foa was appointed Assistant Professor of Physiology at the Chicago Medical School in 1944. Born and educated in Italy, Dr. Foa came to this country in 1939 possessing a thorough and enviable academic background. During his comparatively short stay at the Chicago Medical School, he has added to his achievments in both this country and abroad, the following:

Member of American Physiological Society.

Member of the Society for Experimental Biology and Medicine.

Editor for the United States and Canada of Resenha Clinico-Cientiefica of S. Paulo, Brazil.

Secretary for the Chicago Section of the American Committee for Medical aid to Italy.

Dr. Foa has been awarded two, two-thousand dollar grants by the John and Mary Markle Foundation for Medical Research of New York, for studies on the relationship of thiamine and insulin, to be carried out in 1945 and 1946.

In addition he has delivered the following addresses:

Transmethylation, delivered before the University of Illinois Physiology Journal Club.

The Relation of Chemical Structure to Biologoical Activity, also delivered before the University of Illinois Physiology Journal Club.

Besides the above accomplishments Dr. Foa has also found time to write the following publications:

A Simple Method for the Determination of Effective Renal Blood Flow and Tubular Excretory Mass in Man. ibid., 211.

The Effect of Nicotinic Acid and Nicotinamide in Growth, Liver Fat, Renal Hemorrhages, and Excretion of "Trigonelline" in the Rat. Arch. Biochem., 1945, 6, 215.

The Urinary Excretion of Trigonelline and Nicotinic Acid in Human Subjects after the ingestion of Trigonelline and after smoking. In press.

The Formation of Nicotinic Acid-like Substance from Trigonelline in Man. In press.

The Quarterly staff also wishes to extend their heartiest congratulations to Dr. and Mrs. Foa on the birth of their daughter, Helen Serena, born Dec. 21, 1944.

The Physiology and Pharmacology Department of the Chicago Medical School wishes to acknowledge the addition of two new members to the Department. Miss Harriet Weinstein has been working as Research Assistant in the Department of Physiology and Pharmacology since October, 1944. Miss Mildred Wolff has also joined the Department of Physiology and Pharmacology as Technical Assistant and has charge of the stock room. The *Quarterly* extends a hearty welcome to both.

During the mid-quarter vacation, Dr. Louis Plzak attended the Mayo Clinic, at Rochester, Minn. Drs. Congdon and MacFarland attended the regional meeting of Anatomists at the University of Iowa. In an interview with Dr. Congdon it was disclosed that the meeting was the last regional meeting that was to be held, and that hereafter, they will return to the former practice of holding yearly meetings. The purpose of these meetings is to present the results of recent investigations. Two men presented papers at this regional meeting. The first was submitted by a surgeon who presented the results of a recent study he made on the remapping of the areas and, distribution of the dermatomes. The results were based upon studies made on patients who presented themselves with hernias of the nucleus pulposus which compressed a single spinal nerve. In these cases the nucleus pinched a single spinal nerve against the pedicle of a vertebra. The second paper was presented by Dr. Congdon who presented a final report on results of a study of the subcutaneous layers in the anterior and lateral trunk by means of razor cuts. The chief topic of interest was the fibrous sheath in the subcutaneous layer. There are five different views as to its character. The accounts in the English language are fifty percent wrong for two chief reasons: firstly, the sections studied vary with the adiposity of the specimen, and present workers have only grouped bodies according to the scheme of thick, intermediate, and thin subcutaneous layers. Secondly, no one has ever previously studied its character by use of cross sections, except to a very slight degree. It is so delicate in structure that dissection distorts it in various ways. It is found to be highly variable in the details of its distribution and as to how definitely it forms a well defined, clear cut sheet. On the whole, Dr. Congdon reports, for the anterior and lateral trunk, it is most constant and complete laterally; and better developed in the abdomen than in the thorax.

Organizations

Phi Lambda Kappa—in Review for 1945

THE activities of the Alpha Rho Chapter began with an auspicious dinner-meeting at the Illinois Union at which greetings were presented to the alumni guests, Drs. Kaplan, Block, and Rosenberg. Dr. Rosenberg of the Department of Dermatology at the Chicago Medical School spoke on the importance of mycology in medicine and showed interesting illustrative colored slides on the subject.

On February 14, the chapter was proud to welcome Dr. Maxamilian Weinberger, faculty member of our institution, into the Phi Lambda Kappa Fraternity at a meeting and smoker held in conjunction with the Alpha Alpha chapter of the University of Illinois. It proved to be a grand event with many alumni present and many expressions of congratulations to Dr. Weinberger, and in addition the meeting was under the able chairmanship of the Chicago Fraternity Alumni head, Dr. Bernard Horwitz. We and those before us who have been in contact with Dr. Weinberger and have profited from his teachings in medical diagnosis are convinced that benevolence, sincerity and kindliness bespeak the man. The meeting was also marked by the appearance and words of two of the nationally honored fraters, both of Chicago; Dr. W. Schiller, Pathologist at the Roseland Hospital, and Dr. M. Oppenheim, Dermatologist-in-chief at the Chicago Medical School. The latter gave a warm and hearty welcome to his comrade, Dr. Weinberger, revealing a friendship between them that took origin in an anatomy dissection room in the Univesity of Vienna 40 years ago. Among the other speakers were Dr. J. Brodsky, Dr. M. I. Kaplan, G. Pollack, President of the Alpha Alpha Chapter, and our own Worthy Superior, B. W. Rockliff.

On March 4, eleven prospectives were accorded full membership in the fraternity and were greeted as new members by Dr. W. Rosenberg and Dr. B. Horwitz. The latter also presented a fascinating account of his experiences in the Navy during the past two years. Congratulations to our new Fraters: W. C. Feldman, M. Leichtling, A. H. Rothenberg, L. Ruff, M. Werner, B. Bodell, B. Cutler, J. Ehrlich, L. B. Epstein, J. Seskind, and R. R. Simner. We hope that all of you will take an active part in the affairs of Alpha Rho, and will help spread the true fraternity spirit.

On July 8, at the Hotel Morrison, Alpha Rho greeted the new freshmen, and a gay informal smoker was held. Several faculty members were introduced to the neophytes, and short speeches on the problems facing a new medical student were presented. Among the speakers were Drs. Levine, Nice, Ryan, Smith, Foa, and Dreikurs—all on the faculty of our institution. Dr. Levine emphasized the importance of compromise in order to get along well with our fellow men, and Dr. Dreikurs proposed the following principle for the Physician: "Do not be discouraged and do not discourage."

Several more Fraters have taken Cupid seriously, and to those, Alpha Rho extends its best wishes and the best of luck. The recently married include:

Stan Menachof to Miss Janet Abraham of Cincinnati, Ohio; Harold Koenig to Miss Ruth Steinman of Chicago; Sidney Malitz to Miss Lucille Dvorsay of Hammond, Indiana; Alan C. Siegal to Miss Corinne Quint of New York; Clarence A. Peckler to Miss Ruth Goldstone of Chicago; Leo Ascher to Miss Jayne Wiesenberg of Cleveland, O.

And the recently betrothed include:

Gerald J. Rabinovitz to Miss Annajean Kornblatt of Chicago; Murray Feldman to Miss Mildred Milstine of Chicago.

* * * * *

Psychosomatic Disease—

(*Continued from page* 6)

dated from the emotional stress of military action.

In view of the numerous diseases in which psychogenesis may play a part, the taking of a careful history upon each patient becomes a procedure of greatest importance. Charcot once said: "In dealing with a nervous patient—you should regard the malady before you merely as an episode in the history of the disease." The danger of diagnosis upon the basis of the present physical and clinical findings alone is obvious.

It is the duty of the physician to study each case as a disease entity involving both the body and mind of the patient, lest the criticism of Cruickshank become a deserved one: "—well-meaning practioners often remove organs seriatim until the neurosis is left solus like the grin of a Cheshire cat."

Abstracts

THE ANXIETY NEUROSES MANIFESTED BY GASTRO-INTESTINAL SYMPTOMS

Capt. Alexander Rush, Med. Corps A. U. S.
The Med. Clinics of N. Amer. Vol. 28, Nov. '44, p. 1541-53.

THE most frequent types of psychoneuroses noted in an Army hospital report of the first year of our war in the Pacific, were those associated with symptoms of the gastro-intestinal tract. The clinical pictures were extremely variable consisting of poor sleep, bad dreams, easy fatigue and depression, these manifestations of uneasiness being reflected in protean types of associated gastro-intestinal complaints. Most commonly found were migratory lower abdominal cramps appearing shortly after food ingestion and relieved spontaneously within an hour or after bowel movement. Feelings of fullness on eating with easily discernible borborygmi were also frequent. Often seen were nausea and vomiting during or after eating and pain simulating peptic ulcer in the epigastrium. In spite of these symptoms, however, these patients characteristically *rarely* showed evidence of malnutrition or weight loss.

Physical examination revealed tenderness over the large bowel and sigmoid in about one-third of the cases. This finding, along with the symptoms listed above, an apparent anxiety or other unstable manifestations, and *negative* X-ray, proctological, and stool examination, were the important points in diagnosis.

Differential diagnosis always presents a great problem in neurosis, and so it did in this case. Peptic ulcer was the most difficult condition to rule out, but history, gastric analysis, X-ray, response to alkaline treatment, and induction of typical ulcer pain upon HC1 introduction which was relieved by $NaHCO_3$, were decisive factors Gastritis, dysentery, appendicitis, and gall bladder disease were all considered.

Treatment consisted first of all of a sympathetic attitude by the physician to gain the confidence of the patient. If at all possible, the patient was made to understand the realness of his condition despite absence of organic lesions, and the relation between such common emotions as anxiety, fear, and resentment to digestive disturbances made clear. Specific measures as bland diets, sedatives, and antispasmodics were also found useful.

The author points out that the great emphasis of modern advertising on making the public conscious of possible gastro-intestinal diseases has aided in focussing many of the present day neuroses on this system. In situations such as military life, poorly integrated emotional systems are confronted with overpowering new responsibilities, environments, and new fears, the outlet for which gains ready access to neurotic symptoms.

In the milder cases, explanations and reassurance supplemented by symptomatic measures, were sufficient. The chronic confirmed psychoneurotic, however, had to be removed immediately from his position of stress in military work, the problem being a much deeper and more prolonged one in his case. It is of great significance that a large majority of these neurotic patients fell in the lowest two groups of the Army Intelligence Classication Test.

In neurotic conditions, as in so many other medical problems, the imperative nature of early recognition is the most important factor in the prevention of an extremely refractory and unfortunately permanent disease. —S. I.

* * * *

RAPID DEVELOPMENT OF CARRIER STATE AND DETECTION OF THE POLIOMYELITIS VIRUS

Gordon C. Brown, Sc.D., Thomas Francis Jr., M.D., Harold E. Pearson, M.D.

It is a well established fact that the poliomyelitis virus may be demonstrated in the stools of a high percentage of cases of the disease and may be present for weeks or months after the onset of the clinical condition. Presumptive evidence of harboring the virus for a considerable period prior to the disease onset has also been advanced with special reference to positive nasopharyngeal washings of children who had been in contact with a later developing case and who themselves later showed manifestations of the disease. One report of positive stool specimen for the virus had been reported in what turned out to be an abortive case 11 days following the stool collection.

This report concerns a study made in a children's summer camp near Detroit, in which stool and nasopharyngeal specimens were taken of all children in contact with a boy who had the onset

of his disease just 5 days after his arrival at the camp. 19 days after the detection of the polio virus in the stools of one of these boys, he developed typical signs and symptoms of poliomyelitis. It was established that no other source of the virus could have been responsible for the later development of the second case.

The stool specimens were tested by monkey inoculation performed intracerebrally, intraperitoneally, and intranasally over graded periods of time. These caused typical paralytic developments and later microscopic findings of characteristic perivascular cuffing and infiltration, neuronophagia and cytolysis.

This case establishes the fact that the poliomyelitis virus may be present in the intestinal tract for a considerable period of time before the onset of the paralytic disease. Important is the fact that the virus was recovered from the patient's throat washings on the day after hospitalization but not one week later. This agrees with findings of others which indicated that a positive specimen from the nasopharynx was common at the disease onset but uncommon five days later, showing that this is not an important source of infection following one week after the beginning symptomatic evidence of the disease. The possible conclusions to be drawn from this report are that the presence of the virus in the nasopharynx is associated only with the early stages of the acute phase of the disease, while the intestinal tract is a potent source of the virus before, during, and for some time after the onset of clinically diagnosed acute anterior poliomyelitis.—S. I.

Book Review

Nervousness, Indigestion and Pain by Walter C. Alvarez, M.D. 488 pages. Paul B. Hoeber, Inc., 1943, New York City, N. Y.

THIS is a different sort of a book" reads the first line of the preface to this medical gem written by one of the foremost physicians of our time. And so it is. For here is medicine presented to us by a doctor who is at once our friend, our teacher, and our guide.

Written in a simple and systematic order, this work presents the personal views of a master artist and scientist gained from years of clinical experience, study, and laboratory experimentation. The all too confusing conditions of migraine, dyspepsia, constitutional inadequacy, allergy, constipation, mucous or spastic colitis, and many others presenting "pseudo" pictures, are frankly discussed and elucidated, and our present knowledge is evaluated in the light of the vast experience of the author and his associates at the Mayo Clinic.

Aside from the extremely helpful suggestions in diagnosis and treatment offered which are not found in the usual standard textbook descriptions, this book stands as a milestone in medical literature for still another very important reason. This is the stress laid upon the effects of emotions on the development of symptomatic manifestations of disease when no signs of actual organic lesions can be found. To Alvarez must go a large part of the credit for bringing to the fore the great importance of neurotic tendencies found in clinical practice. What others had only hinted and mentioned fleetingly, he had the fortitude to proclaim. Rarely does one find the great stress of diagnosis of the patient, aside from the disease, as one does here.

The absolute necessity for all physicians to understand fully the underlying bases of neuroses and their various manifestations, is repeated over and over again in the undeniable manner of presenting a large number of actual cases which show lucidly the great frequency of such problems.

Although many psychologists and psychiatrists may disagree with some of the explanations and therapy outlined by Alvarez, none will deny the great contribution he gives to medicine in this book, by bringing to light the omnipresent reality of problems of neuroses in all branches of clinical medicine. Following mostly the psychiatric principles of psychoneuroses outlined by T. A. Ross, the author embodies these and expresses their meaning in the numerous examples described.

To the practicing clinician, this book is recommended as an indispensable guide and reference, simply explained and presented. For the medical student, it is an extremely valuable and interesting adjunct to the more routine text book study. For all whose interests and work require a knowledge and comprehension of the correlation between disease and the psychological makeup of the patient as an individual, this outstanding work must rank as one of the finest aids toward grasping reality in a subject heretofore clouded with distortion and vagaries. —S. I.

Chemical Structure—

(*Continued from page* 16)

mine is capable of neutralizing the growth-promoting action of one mole of thiamine. Woolly and White studied the action of pyrithiamine on many bacteria, yeasts and fungi and found inhibition of the growth of only those species which require thiamine to grow. Approximately 10 molecules of pyrithiamine were found to be necessary to neutralize the growth-promoting action of one molecule of thiamine for microorganisms. Woolley and White also found that the administration of pyrithiamine to mice produces a fatal disease similar to thiamine deficiency, which can also be prevented or cured by thiamine. In this case 40 molecules of pyrithiamine are necessary to nullify the action of one molecule of thiamine. The animals treated with pyrithiamine fail to grow and lose weight, at the fourth or fifth day they become inactive, assume a hunched posture, develop tremors and occasional convulsions, weakness and then a complete paralysis of the legs. No mouse survives more than 3 days after the onset of symptoms.

Pyrithiamine can take the place of thiamine not only in the enzyme system connected with the metabolic processes, but also in those by which thiamine is destroyed. It is known that a diet of raw fresh-water fish will produce fatal thiamine deficiency in cats and other animals. Fresh-water fish contains an enzyme, the so-called Chesteck paralysis factor, which destroys thiamine. It has been demonstrated by Sealock and Goodland that pyrithiamine can occupy the place of thiamine on the surface of this enzyme and protect thiamine from destruction, a brilliant, although indirect, confirmation of the theory according to which inhibitor and promoter analogues act by competing for the enzymes necessary for growth and for life.

Riboflavin—In a similar way slight modification in the chemical structure of riboflavin results in the production of analogues having an antiriboflavin activity. Thus Kuhn, Wieland and Moeller obtained inhibition of bacterial growth with 6,7-dichlororiboflavin, a substance obtained by substituting two Cl. atoms for two methyl groups. The simple changing of the position of the two methyl groups is sufficient to produce a competitive analogue of riboflavin. Emerson and Tishler found that isoriboflavin, having the methyl groups in positions 5 and 6, inhibits the growth of microorganisms and of rats, in competition with riboflavin, the methyl groups of which are in positions 6 and 7. (XIII & XIV).

Similar results were obtained by Woolley (1944) by substituting two carbon atoms for two nitrogen atoms in the riboflavin molecule, thus converting a purine into a benzimidazole ring (XV).

Biotin—The structure of biotin was announced by Du Vigneaud at the October 9, 1944, meeting of the New York section of the American Chemical Society. During the studies following this important discovery Du Vigneaud and his collaborators prepared a number of biotin derivatives and found that some of them possessed antibiotin activity. Among these is biotin sulfone which inhibits the growth of L. casei in competition with biotin. Desthiobiotin, a product derived from biotin by replacing the sulphur atom with two hydrogen atoms, has the same effect on L. casei and other microorganisms (Dittmar, Melville and Du Vigneaud; Lilly and Leonian). The substitution of the methyl group attached to the imidazolidone ring of biotin with caproic acid results in a product which does not promote but inhibits the growth of yeast. The presence of a methyl group thus makes a vital difference. The compound is also an antibiotin for L. casei, E. cali and Pneumococcus types II and III. This fact enhances the role that this biotin derivative may play as an antivitamin and gives hope that a chemotherapeutic agent might be developed along these lines. In a manner similar to that which applies to pyrithiamine and the raw fish factor, Du Vigneaud found that avidin, the antibiotin factor present in raw egg albumen, inhibits the action of biotin sulfone, of desthiobiotin and of the caproic acid derivative. The addition of these substances to a yeast culture in the presence of avidin-bound biotin displaces some of the biotin which then becomes available for the growth of the organism, again indicating a competition between promoter and inhibitor for the combination with avidin.

Ascorbic Acid—Mice and cotton rats can grow and live on a diet completely deprived of ascorbic acid. If, however, glucoascorbic acid (XVI & VIII) is fed, scurvy will develop and the animals will die within two weeks with diarrhea and hemorrhages of the costo-chondral junction, the joints, gums and lungs. Glucoas-

corbic acid prevents the utilization of ascorbic acid of dietary as well as endogenous origin. Ascorbic acid will not prevent the disease, but fresh cabbage will. Woolley and Krampitz, the authors of these experiments, conclude that glucoascorbic acid acts by blocking not ascorbic acid, but some product related to it in its normal process of utilization, in a manner similar to the action of monoiodoacetic acid in the metabolism of glucose. In the guinea pig, an animal whose health requires the presence of ascorbic acid in the diet, vitamin C will counteract the scorbutogenic action of gluecoascorbic acid (Woolley, 19444).

Miscellaneous Compounds — Overman, Field, Baumann and Link found that a daily administration of 1.5 to 2 mg. of coumarin to rats produces a marked reduction in prothrombin activity, followed by death in 14 to 29 days. The animals look ill, cold, develop paralysis of the hind legs, failure of the blood to clot and spontaneous diffuse external and internal hemorrhages. Vitamin K (2-methyl-1-4-naphthoquinone) counteracts completely the action of coumarin. The similarity in the structures of the two compounds is apparent (XVIII & XIX). It is interesting to note that dicoumarol possesses antibacterial properties (Colwell & McCall) and that it is found in spoiled sweet clover. If it could be proved that dicoumarol is formed by microbial action, it could be considered a natural antibiotic and classified together with penicillin (Goth). This hypothesis is strengthened by the discovery that some antibiotics produced by molds have a quinone structure (Armstrong, Spink, and Kahnke; Oxford and Raistrick), and that iodinin, the natural antibacterial substance produced by the Chromobacterium iodinum, is counteracted by certain anthraquinones, napthaquinnones and by vitamins K_1 and K_2 (McIlwain, 1943). It is believed by many that most bacteriostatic agents act by interfering with the metabolism of some essential substance, by combining with it chemically or by competing for the same position on the surface of essential enzymes by virture of chemical similarity (Anderson).

Bell and Roblin have formulated a theory of the relation of structure to activity of the sulfanilamide type compounds. Starting from the assumption that the bacteriostatic action of the sulfa drugs is due to a competition with the paminobenzoic acid needed for bacterial growth, they postulated that the closer the competitor resembles PABA the greater should be its action. Studying some physico-chemical properties of PABA and of various sulfadrugs, they found that as the acid dissociation constant of the antibacterial agent increases, its activity passes through a maximum and then decreases toward zero. The authors have synthesized products having a predicted acid dissociation constant and have found that they had the predicted bacteriostatic activity. A quantitative relation between structure and activity was thus established and the postulated explanation for the antagonism between promotor and inhibitor was given strong experimental support. The rather startling conclusion reached by Bell and Roblin is that better bacteriostatic agents probably will not be found because the ones already in use are very near the top of the curve relating structure to activity. This does not exclude the possibility that new antibacterial compounds may be found having some practical advantages such as better solubility or smaller toxicity.

Summary and Conclusions — An attempt has been made to summarize recent experiments illustrating new aspects of the old topic of the relation of chemical structure to biological activity. The experiments deal with the antagonistic and competitive properties of many essential dietary factors, such as vitamins and aminoacids, and substances with similar chemical constitution. These studies have given us a better understanding of the mechanism of action of antibacterial compounds of their optimal dosage and have opened new ways of obtaining antibacterial agents and antivitamins. It might lead to the discovery of products with antihormonal properties useful in the treatment of diseases due to hypersecretion of the endocrine glands.

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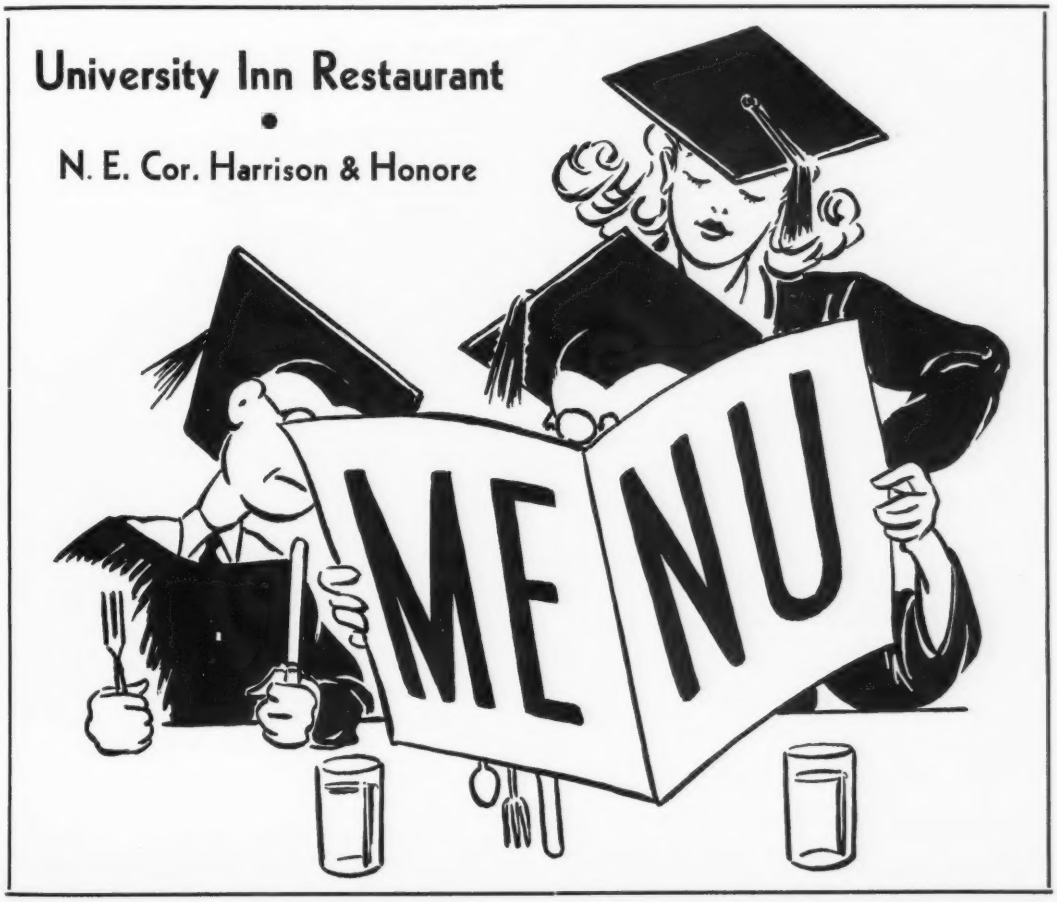
* * * * *

CASE No. 166—Dear Colonel: What is your favorite part of the Bible? Sky Pilot. *Answer*: The chapter that describes how God first created the universe and rested; then He created man and rested; finally he created woman, and since then neither God nor man has rested.



sional donors without reaction. Subsequent typings were as follows: Patient Group O Rh—; Husband Group O Rh+; Brother-in-law Group O Rh +; Sister Group O Rh—; Brother Group O Rh—.

One can easily conclude from the given data that the patient had been sensitized by the transfusion of the husband and brother-in-law. On re-transfusion of the antigenic Rh+ blood to the woman who had developed the anti Rh agglutinin, the hemolytic reaction occurred.

Many more cases, similar in nature, could be avoided and shall be done away with when hospitals institute in their usual typing procedure the policy of also determining whether or not there is any Rh incompatibility involved in the transfusion.

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Erythroblastosis—

(*Continued from page* 18)

ple as it was when first discovered, for changes and more details being added by Wiener (10,12) and those men working on the problem today. The simple description, however, should not be cast aside for it makes one more easily visualize the mechanism of inheritance. Just as agglutinogens A, B, AB and O are genetically determined by the combination of any two of three allelic genes I*a*, I*b*, and i, different types of Rh have recently been found; and these seem to be determined by a series of allelomorphs Rh_1, Rh_2, Rh', Rh", Rh*o* and rh, all of which are named after the agglutinogen which they determine.

The study of the Rh factor was not delimited to only a fetal condition for its importance in normal transfusions was immediately recognized. The existence of a negative reaction on the part of the patient in many cases of transfusions, even after blood typing for the common agglutinogens, immediately brought up the question as to whether or not Rh was the solution to the problem. It was found that men and non-gravid women did not show, after sensitization, the same reaction that a gravid woman displayed, for when a transfusion was given to an isoimmunized gravid woman, one might have to contend with serious, chronic and possibly fatal complications. A typical case(13) might more easily show the importance of this factor in transfusions.

A 26-year-old woman, with recurrently severe anemia secondary to menorrhagia, in 1939 received a 500 cc. transfusion from her husband, and three days later a 600 cc. transfusion from her brother-in-law, neither being followed by a reaction. Six months later she was given another transfusion from her husband which was interrupted at 300 cc. because of pain in the flanks and dyspnea, subsequently hemoglobinuria developed. Two days later she received a 600 cc. transfusion from her sister without reaction. One week later another transfusion from her brother-in-law was begun and this was interrupted after only 200 cc., because of severe dyspnea and signs of shock; anuria and jaundice appeared within 24 hours. One day later she received a 600 cc. transfusion from her brother without reaction. In 1941 she was given two transfusions totaling 1300 cc. from profes-

(7) De Lee, Greenhill—Principles and Practice of Obstetrics.
(8) Idem.
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* * * * *

Vitamins—

(*Continued from page 5*)

duce the lesions corresponds to a dose of 1 or 2 grams for an average man. Doses of one half gram are often used in therapy for long periods of time and it is not impossible that they might result in liver damage. Nicotinic acid is excreted in the urine mainly in the form of methylated derivatives (Trigonelline and N-methyl-nicotinamide). Evidence is at hand showing that probably the methyl groups necessary for this biological synthesis are derived from the same pool from which other methylated compounds draw and that excessive amounts of nicotinic acid deprive the organism of methyl groups and produce or aggravate the symptoms of methyl group deficiency. These are: fatty infiltration of the liver, renal hemorrhages and inhibition of growth. They can be prevented or cured by the administration of "Methyl donors," such as methionine or choline.

Vitamin D—It is hardly necessary to describe in detail the symptoms of hypervitaminosis D which have been known for a long time. According to Goodman and Gilman; Harris and Moore; Rose and Sunderman, an excess of vitamin D will produce anorexia, vomiting, abdominal cramps with diarrhea, thirst, loss of weight, vertigo, tinnitus, degeneration of the kidneys and death. The disease is associated with a decalcification of the bones, excessive excretion of phosphates, hypercalcemia and diffuse calcifications in almost all organs and tissues, especially kidneys, stomach, lungs, heart, blood vessels, and bronchi.

Vitamin K — The natural form of vitamin K_1 and K_2 apparently are not toxic; their synthetic substitutes, 2-methyl-1-4-naphthoquinone and 2-methyl-1-4-naphthohydroquinone, however, produce vomiting, porphyrinuria and albuminuria, if given in oral doses of 180 milligrams in man or 3 to 60 milligrams per kilo of body weight in the

(*Continued on page 40*)

Licensed Physician—

(*Continued from page 26*)

ton Medical Library there is an almost complete file of everything he ever wrote, much of it in the original manuscript and in his own handwriting.

S. WEIR MITCHELL was another. He was both a popular writer and a great doctor. He wrote voluminously both on medical and popular topics. In medicine he is known as the originator of the "rest cure." He was a famous neurologist and some traces of this can be seen in his popular novels.

JOHN McCREA, the Canadian, was a poet who wrote one great poem *"In Flanders Fields,"* for which he will always be remembered. He studied medicine at Toronto. In 1899 he was appointed Pathologist at McGill University, later he lectured in clinical medicine. He died of pneumonia soon after his appointment as consulting physician of the British forces in the field, World War I.

CHARLES ALEXANDER EASTMAN, a real American as he is a full-blooded Indian, has written some of the best stories of American Indian life. And he has translated many of their folk songs into English and set them to music, or as nearly as our musical scale approximates that of the Indian scale.

Many other American physicians have attained fame as writers of other than medical theses. Several of them deserve mention. Dr. John R. Oliver both doctor and priest; he is a psychiatrist, a priest and a professor of medical history at Johns Hopkins University as well as a novelist of power.

Helen Johnson is the only woman among the long list of whom I have given you a few names. She writes under the name of *Helen Ashton* and is a writer of repute and a practicing physician as well, married to a doctor.

The best detective story writers have been physicians. Probably trying to solve medical problems and making snap diagnoses has fitted them especially for the role.

So do not become discouraged if patients are slow to come. Who knows, there may be a second Shakespeare among you.

* * * * *

If the trend toward centralization continues at the same rate, what will become of state governments? Will they become merely historic vestiges like the urachus or the obliterated hypogastric arteries? —Virginia M. Monthly

Cor Pulmonale—

(*Continued from page* 13)

Positive heart findings sometimes found are cardiac arrythmia, a pulmonic systolic murmur, accentuated pulmonic second sound, and low systemic blood pressure.

Electrocardiographic and roentgenographic evidence may have to be utilized before a definite diagnosis is made. The electrocardiograph shows abnormal right axis deviation. 17. It is often difficult to find right ventricular enlargement by means of the roentgenogram. An anterior-oblique view of the heart may be of help in this case, and a fluoroscopic examination may show extreme pulmonary artery dilatation.

The prognosis of the chronic cor pulmonale is that of the underlying pulmonary condition. Its onset is insidious. Death is rarely due to right heart failure in this case. In the case of chronic cor pulmonale due to endarteritis obliterans, death from heart failure will take place from a few months to a few years.

The important complication of chronic cor pulmonale is right heart failure. In about half the cases, coronary heart disease has been found to occur. This is probably due to the advanced age of these patients. 1.

The treatment of chronic cor pulmonale is that of treatment of the chronic pulmonary disease, and/or heart failure, when it occurs, with bed rest, digitalis, diuretics, and symptomatic treatment. Oxygen inhalation may be very beneficial because of the pulmonary disease. White suggests administration of a test dosage of digitalis on purely empirical grounds. He suggests that if it is of benefit, its use should be continued.

Other therapeutic measures are: (1) care to prevent any further respiratory infection by avoidance of fatigue and by residence in a dry climate; (2) anti-luetic therapy when it is the cause of endarteritis obliterans.

Advance in thoracic surgery holds out hopes for treatment of chest deformities and pulmonary diseases which may be the underlying causes of cor pulmonale.

The two conditions from which it is often difficult to differentiate chronic cor pulmonale are the pulmonary disease itself and congenital heart disease without the characteristic murmurs. The presence of the emphysema, and the absence of any history of heart difficulty or cyanosis in childhood should be sufficient to differentiate the two. The response to digitalis may help identify the pulmonary heart disease. Mitral stenosis, which sometimes has to be differentiated can be identified by the characteristic apical diastolic murmur. Pulmonary endarteritis obliterans may be distinguished by its appearance in young people without pulmonary disease, by its accompanying intense cyanosis and by its rapid downhill course. 1.

* *

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Liquid Ammonia—

(*Continued from page* 10)

descriptions of chemical treatments which prolonged the action of naturally occurring hormones, that were described in scientific journals of national prominence. Both products had been described previously, however, before Danish and American scientific societies. (Nordisk Congress for Internal Medicine at Copenhagen, 1935, and Society for Experimental Biology and Medicine at Chicago, 1934).

Hagedorn and Jensen used the protein protamine for conjugation with insulin in order to prolong its action; other workers used different proteins such as globin for the same purpose. Their work was successful in that they prolonged the action of a hormone, but they accomplished this result by introducing foreign proteins into the body. Such proteins sometimes bring about reactions or protein shock and some patients cannot tolerate a conjugated insulin of the types described at all. In order to overcome this defect an attempt was made to conjugate insulin with non-protein substances in liquid ammonia. Crystalline insulin is soluble in liquid ammonia and no inactivation of the hormone occurs after an exposure of 24 to 48 hours. Since good results had been obtained by conjugating adrenalin with certain amino acids such as glycine, this amino acid among others was used in an attempt to form a prolonged acting insulin. The bio-assay indicated little or no prolongation although the activity of the insulin was not destroyed. When the amino acid cysteine was used, however, complete inactivation of the insulin occurred. The inactivation in this case was probably due to the reducing action of the cysteine. Several other compounds were used, the most successful of which was hemin. In United States and Canadian patent applications the preparation of this conjugate is completely described.

The action of liquid ammonia upon certain micro-organisms had also been studied. As far back as 1931 an attempt to extract an exotoxin from *B. coli* was made by carrying out the extraction in a closed system of DeWar flasks, using sintered glass filters. The results were negative; no exotoxin was obtained. Within the last year or so the tubercle bacillus has been treated with liquid ammonia or with dry ammonia gas. Both the liquid and the gas kill the bacillus. The ammonia treated T.B. will elicit a positive tuberculine test.

The latest compound to be studied in liquid ammonia has been penicillin. The data from this work, however, has not been fully collected or analyzed at the present time. But a story beginning with Ammon Ra and ending with penicillin is a long one as far as the distribution of time is concerned and as the geologists say when they have traced the history of the earth down to the cenozoic age: "This is where we get off."

Letters to the Editor

October 14, 1945.

The Editor of the Quarterly,
Dear Dr. Malitz:

Thank you very much for sending me the latest issues of the Quarterly. I enjoy reading it in my spare time, and I find it an excellent instrument of contact with the School's activities, and with the progress of my old classmates.

I am now associated in private practice with the well-known Chicago internist and specialist, Dr. Eugene F. Traut, F.A.C.P., Professor of Clinical Medicine, University of Illinois.

Cordially yours,
Herman Frack, M.D., Class of Dec. 1943.

* * * *

Liege, Belgium
10 June, 1945

The *Quarterly*
The Chicago Medical School
Gentlemen:

Kindly note the change of address to the above. I have been overseas about three months and have been doing neuropsychiatric work for about a year and a half.

I would like to get on record that I was married July 30, 1944 to Miss Veda L. Burks, schoolteacher, of Arkansas City, Kansas, when I was on the Winter General Hospital Staff, Topeka, Kansas. Following this experience, I would heartily suggest marriage to anyone who has found the Right Girl!!!

Keep up the good work. I enjoy *"The Quarterly"* immensely. Kindest regards to Dr. Sheinin and Staff.

Sincerely,
George E. Fisher,
1st Lt. M. C.

Social Notes—

(*Continued from page* 19)

Joe DeCaro and Violet Ingraffia were married September 16, 1945, in Chicago.

Phil Deaver and Elthia Sample of Grand Island, Nebraska, were married in June, 1944.

Harold Koenig and Ruth Steinman were married February 11, 1945, in Chicago.

* * * * *

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Miss Campbell wishes to express her appreciation to all those who helped her in putting over the Drive in the school. The Red Cross has given credit to the school for the above amount.

* * * * *

SHOULD VITAMIN D BE GIVEN ONLY TO INFANTS?

Vitamin D has been so successful in preventing rickets during infancy that there has been little emphasis on continuing its use after the second year.

But now a careful histologic study has been made which reveals a startling high incidence of rickets in children 2 to 14 years old. Follis, Jackson, Eliot, and Parks* report that postmortem examination of 230 children of this age group showed the total prevalence of rickets to be 48.5%.

Rachitic changes were present as late as the fourteenth year, and the incidence was higher among children dying from acute disease than in those dying of chonic disease.

The authors conclude, "We doubt if slight degrees of rickets, such as found in many of our studies as a whole afford reason to prolong administration of vitamin D to the age limit of our study, the fourteenth year, and especially indicates the necessity to suspect and to take the necessary measures to guard against rickets in sick children."

* * * * *

How little do they see what is, who frame
Their hasty judgments upon that which seems.
—Robert Southey

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We are really very modest—

but it is no use denying that we are very pleased with, and slightly proud of, the way you have received the QUARTERLY. Your letters have been unanimously complimentary, your comments heart-warming. We thank you.

Especially do we derive deep satisfaction from supplying to you who are in the armed forces the measure of diversion and enjoyment that you have told us the QUARTERLY brings you. We intend to get the QUARTERLY to you, wherever you are, if it is at all possible, and whether or not you are active subscribers. Thus, we may feel that we are helping you, in a very slight way, to do the grand job that you are doing, at and behind the fronts.

But the QUARTERLY cannot be published with good wishes alone. We ask those others of you, who are fulfilling the equally important task of maintaining civilian health, to support this publication so that it may continue to bring you and our graduates in the service into closer touch with The School and each other.

Sincerely,

The Editor

I hereby enclose (a check for) $..... (1 year's subscription, $3.00)
(2 year's subscription, $5.00)

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Vitamins—

(*Continued from page* 35)

dog (Goodman and Gilman). Ansbacher, Corwin and Thomas found that the daily administration of menadione or menadiol in the dose of 50 milligrams per kilo in the dog produces anemia and hemoglobinuria. According to Field and Link much smaller doses of 2-methyl-1-4-naphthoquinone (1 to 4 milligrams per kilo) produce a state of hyperprothrombinemia with increased coagulability of the blood, which last for several days and can, in turn, produce thrombosis and embolism.

It appears from this brief discussion that many of the vitamins commonly used in human therapy are not completely harmless and that their indiscriminate use can be dangerous.

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